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"ASSESSING THE SEVERITY OF POISONING FROM NARCOTIC AND PSYCHOTROPIC SUBSTANCES".

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Currently, cases of opiate and psychotropic substance poisoning are constantly increasing. They occupy an important place both in the total number of all poisonings and in the entire forensic medical structure of death. Publications on this topic indicate a sharp increase in cases of overdose of such substances.

This monograph is intended for practical use in lecturing for forensic medical experts, as well as students and master's students of medical universities.

CONTENTS

FME – forensic medical examination

CIS – Commonwealth of Independent States

UN – United Nations

WHO – World Health Organization

TDSII- Thermal desorption surface ionization indicator

INPUT

Drug addiction has become one of the most important medical and social problems of our time. Its spread leads to a constant increase in mortality from acute drug and psychotropic poisoning, as well as from complications of chronic drug poisoning.
The history of the emergence, spread, medical use, and subsequent non-medical "development" of opiates dates back at least 5000 years.
Commonly used opiates and psychotropic agents - opium surrogates, morphine and heroin [Tomilin V.V., Salomatin E.M., 2001].

Currently, cases of opiate and psychotropic substance poisoning are constantly increasing. They occupy an important place both in the total number of all poisonings and in the entire forensic medical structure of death. Publications on this topic indicate a sharp increase in cases of overdose of such substances. Due to other causes of death, it is difficult to determine the toxic concentration of opiates and psychotropic substances in the blood and urine of victims. Moreover, the highest number of deaths as a result of acute poisoning with these substances occurs at the age of 17 to 23 years and accounts for 42% of the total number of fatal poisonings [Kandyba T.S. 2007].

The amount of opiate poisoning almost always depends on how we assess morphine levels in urine, blood, and sometimes in internal organs, then to practically resolve the issue of fatal poisoning, it is necessary to clarify the question - can the detected concentration of morphine lead to death? and if so, then with what morphological manifestations should this condition be accompanied? To date, there are no ready-made positions that continue to make decisions about the lethal or lethal concentration of morphine in the blood. There are almost no specialized forensic medical works dedicated to the objectification of expert opinions and the interpretation of forensic chemical research results, where there is a clear and precise parallel between the occurrence of death and the concentration of opiate metabolism products in tissues and organs.

The current understanding of how drug poisoning presents clinically and morphologically in forensic medicine lacks a structured and comprehensive overview. Therefore, the objective is to undertake a thorough investigation, both qualitative and quantitative, to identify novel expert indicators for diagnosing and evaluating the severity of acute drug, and specifically opiate, poisoning. This will be achieved through statistical and sample-based analysis of case histories and forensic examination reports. It is currently evident that detailed information regarding the characteristics of acute opiate poisoning is crucial for advancing the diagnostic capabilities for poisoning cases. Only through such a thorough, evidence-driven methodology can we definitively determine if all instances of detecting opiate metabolites in the environment or in deceased individuals should be categorized as fatal poisonings, or if some represent incidental or background opiate exposure. Gathering this data is particularly vital for enhancing the forensic medical diagnosis of fatal drug and opiate poisonings.

Therefore, the importance of this study stems from several factors:

the widespread non-medical consumption of opiates, frequently resulting in emergencies and severe incidents, a large portion of which end fatally;

challenges encountered in forensic medical assessments of lethal opiate intoxications, particularly in cases involving ambiguous circumstances, insufficiently defined diagnostic benchmarks, and a lack of materials necessary for proper interpretation of toxicological findings;

inadequate understanding of the causal relationships that clarify the variability and sometimes conflicting outcomes of poisoning associated with varying concentrations of opiate metabolites in victims' tissues and organs;

a shortage of investigations into the immediate causes of death, death mechanisms, progression of terminal states, and their temporal evolution throughout different stages of opiate poisoning.

The objective of this research was to perform a toxicometric evaluation of clinical and morphological parameters in cases of acute poisoning by drugs and psychotropic substances, with the aim of establishing quantitative diagnostic criteria and methods for assessing the severity of intoxication.

To accomplish this objective, the following were addressed:

During the years of independence in our country, the level of medical care for the population has qualitatively improved, targeted large-scale measures have been implemented to effectively treat diseases, and modern technologies have been introduced, which have made it possible to obtain tangible positive results. In the study of morphological changes in the liver in acute drug poisoning, large-scale program measures have also been implemented, resulting in new data on organ pathology in drug and ethyl alcohol intoxication. Currently, according to the Action Strategy for the five priority areas of development of the Republic of Uzbekistan in 2017-2021, it is planned to further improve the provision of medical care to the country's population, including forensic medical examinations in cases of acute drug poisoning. Currently, the primary tasks awaiting their solution are timely prevention and diagnosis, and providing high-quality medical care.

Key toxicity indicators for narcotic and psychotropic substances were established.

The diagnostic value of clinical, morphological, and laboratory findings in different opiate poisoning scenarios was assessed, identifying indicators of impending or certain death and their corresponding pathological changes.

The primary pharmacokinetic profiles of the investigated drugs and psychotropic agents were elucidated.

Liver tissue was quantitatively histomorphometrically analyzed in cases of acute and chronic drug intoxication.

While numerous studies in the scientific literature examine various forensic medical facets of drug intoxication (e.g., Shigeev S.V. et al., 2005, 2006, 2007; Novoselov V.P. et al., 2010, 2011(2); Ahmadi B et al., 2014), our review of scientific and medical publications, patent documents, and registration materials revealed a gap. Specifically, there is a lack of dedicated forensic research correlating drug and metabolite concentrations with fatal intoxication outcomes. Furthermore, the presence of psychotropic substances within tissues and organs has not been documented in forensic literature to date.

Contemporary scientific research consistently highlights drug addiction as a paramount medical and societal challenge of our era. Consequently, the accurate identification of acute poisoning from narcotics and psychotropic substances poses a formidable and pressing forensic hurdle. This difficulty stems from several factors: a scarcity of comprehensive case studies on such poisonings, forensic chemical analysis being hampered by minute dosages and the swift metabolic breakdown of potent drugs, and the rapid elimination of toxins from the body through contemporary detoxification techniques. Furthermore, these therapeutic interventions can substantially alter the clinical and morphological manifestations of pathological conditions. The presence of active treatment methods can significantly mask the true state of poisoning, thereby complicating the expert evaluation of acute fatalities in hospitalized individuals, as the complete absence of drugs and the original pathological findings may be obscured.

When death arises from acute narcotic or psychotropic drug overdose during hospitalization, and the possibility of violent death needs to be ruled out, forensic medical determination of the cause becomes significantly more complex. This is because death can stem from a confluence of various contributing factors. While much existing research concentrates on the physical manifestations of drug addiction, acute intoxication from these substances can trigger a wide array of pathological effects and internal organ alterations. Despite ongoing rapid advancements in understanding the development, symptoms, and post-mortem findings of drug and psychotropic poisoning, a comprehensive and practically applicable classification of their clinical and morphological characteristics for forensic medicine remains elusive. Consequently, the objective is to develop new, robust diagnostic criteria for identifying and evaluating the severity of drug and psychotropic substance intoxication through statistical and sample-based analysis of acute intoxication cases and forensic medical reports. Currently, it is widely acknowledged that a deeper understanding of the acute poisoning process is crucial for enhancing diagnostic accuracy.

In forensic medical investigations concerning suspected drug intoxication, the expert's initial step involves determining the necessity of costly supplementary

analyses. A thorough understanding of the forensic medical aspects of these poisonings is crucial for reaching a definitive conclusion. This knowledge, particularly regarding potential complications and prognoses, is paramount in selecting the most appropriate laboratory diagnostic techniques. Furthermore, chemical injuries, unlike many other medical conditions, possess an objective indicator of severity: the concentration of the toxic agent within biological samples. While this offers new diagnostic avenues, it also complicates the interpretation of findings. Consequently, employing quantitative forensic medical standards to evaluate the severity of acute drug and psychotropic substance poisoning, both in living individuals and during postmortem examinations, is essential. From a clinical perspective, existing literature on acute narcotic and psychotropic poisonings highlights the vast range of symptoms, with some individuals experiencing mild cases that do not involve life-threatening chemical damage.

Current methods for diagnosing fatal poisoning primarily rely on post-mortem forensic chemical analysis to identify metabolic byproducts of a chemical substance within tissues and organs. A fundamental misinterpretation arises because any instance where metabolites of a toxic substance are found in blood, urine, or internal organs is often indiscriminately categorized as a death caused by acute poisoning from that substance. Furthermore, proponents of this interpretation of toxicological and forensic chemical findings typically fail to offer any supporting empirical evidence.

This diagnostic strategy introduces both methodological flaws and logical fallacies in inductive reasoning, specifically the "post hoc, ergo propter hoc" error, where a temporal sequence is mistakenly assumed to be a causal one. The alternative, "post hoc non est propter hoc" (that which follows does not necessarily cause), is entirely disregarded, blurring the distinction between mere chronological order and genuine cause-and-effect relationships.

When dealing with cases involving poorly understood or insufficiently researched substances, this approach hinders the objective and accurate determination of the actual cause of death. In such circumstances, justifications

based on convenience or simplifying the role of a medical forensic expert are unacceptable, particularly when they compromise the impartiality of expert opinions and the integrity of medical statistical data.

Research on drug-induced internal organ damage consistently highlights the liver as a particularly susceptible organ. Studies indicate that chronic persistent hepatitis, varying in severity, affects 80% of drug users across all age demographics, with a notably higher incidence in individuals under 19. No correlation between age and the severity of this liver pathology has been established [Kriger O.V., 2001]. Our review of existing literature on liver alterations in drug users reveals a growing body of work, yet the data often lacks completeness and consistency. Specifically, robust and well-supported information regarding the precise role of illicit drugs in the etiology of liver damage remains scarce. Some researchers even propose chronic viral hepatitis as a diagnostic marker for drug addiction [Bogomolov D.V. et al., 2001].

While a patent search uncovered prior research by Kriger O.V. (2001) on somatic pathology in chronic drug poisoning, viral hepatitis remains a prevalent issue among drug users, particularly those who inject. Although hepatitis virus transmission isn't limited to shared needles (e.g., sexual contact, tattooing), this doesn't imply that chronic viral hepatitis (CVH) is the sole diagnosis. This highlights a critical need for distinct diagnostic markers. Therefore, identifying unique characteristics of viral hepatitis progression that are specifically attributable to drug or psychotropic substance intoxication is essential. Such features could form the basis for new forensic medical criteria for diagnosing drug addiction or dependence, as suggested by Pigolkin Yu.I. et al. (2004).

Data published in modern scientific literature indicate that research conducted in Diagnosing the cause of sudden death in drug addicts presents significant challenges. Post-mortem examinations, including gross and microscopic analysis of organs and tissues, frequently reveal a multitude of co-existing health conditions, complicating the identification of a primary cause [Bogomolov D. IN. et al., 2001]. Furthermore, relying solely on laboratory toxicology can be misleading. A substantial proportion (51-53%) of forensic chemical analyses of

biological samples from individuals who died from drug or psychotropic substance intoxication fail to detect the causative agents due to their rapid metabolic breakdown [Pigolkin Yu.I. et al., 2004]. Consequently, forensic medical experts now integrate a comprehensive array of morphological findings with the quantitative analysis of these substances in post-mortem biological samples to establish a diagnosis of drug or psychotropic intoxication [Veselovskaya N.V. et al., 2000]. Research by Pavlenko et al. (2003) has explored the morphological alterations in organs and tissues associated with fatal acute drug poisoning, the structural underpinnings of acute respiratory failure in sudden "heroin" deaths, and mortality patterns across different stages of intoxication.

Concurrently, researchers pinpointed a consistent pattern of disease-related alterations across all cohorts.

For individuals who succumbed before reaching a medical facility, distinguishing features included dermal injection marks, compromised organ perfusion, moderate fluid accumulation in the lungs alongside significant systemic deterioration, and pronounced myocardial damage.

In instances where drug poisoning was substantiated, a novel application of spectral analysis was employed on skin and subcutaneous tissues from injection sites. This analysis revealed elevated levels of iron, silicon, aluminum, lead, and silver, in addition to titanium and chromium, elements typically absent from human skin.

Presently, the primary avenues for post-mortem diagnosis of substance abuse and psychotropic intoxication encompass morphological examinations (standard macroscopic and microscopic analyses, including morphometric techniques), as well as chemical and biochemical investigations.

Among these diagnostic approaches, biochemical methods offer the most advantageous balance of time and financial investment for addressing this specific challenge.

For instance, in cases of drug and alcohol poisoning, markers of renal and hepatic dysfunction, along with the activity of specific enzymes, are assessed.

Nevertheless, definitive biochemical indicators for fatal intoxication remain elusive at this time.

Furthermore, several other factors crucial for gauging the seriousness of acute opiate poisoning warrant specific consideration. These encompass the impact of treatment interventions, the unique physiological traits of each individual, and a multitude of other circumstances and indicators associated with the intoxication.

Consolidating all this information within a unified database system could substantially enrich the data used for forensic medical assessments of fatal intoxications involving drugs and psychotropic substances. We believe its implementation would represent a significant advancement in the field of forensic medicine.

For forensic medical investigations, organizing the clinical and pathological signs of drug and psychotropic substance intoxication is highly significant. This organization could be built upon classifying the clinical and pathological indicators of each specific substance's intoxication based on its concentration levels in the blood of affected individuals. To date, the clinical and pathological presentations of narcotic and psychotropic drug poisonings have not been systematically compiled or broadly applied in forensic medicine. Consequently, the objective is to identify novel diagnostic and severity assessment criteria for drug and psychotropic substance intoxication, both qualitatively and quantitatively, through statistical and sample-based analysis of acute drug and psychotropic substance intoxication case histories and forensic medical examination reports.

Reviewing the scientific and medical literature examined, it can be concluded that, up to now, no specialized forensic medical investigations have been reported in forensic publications that establish a clear link between deaths caused by intoxication and the levels of narcotic or psychotropic substances detected in tissues and organs.

The research encompassed data from 422 survival cases and 191 fatal instances of acute poisoning involving narcotic drugs and psychotropic agents.

For the epidemiological analysis, archival records from the Tashkent City Bureau of Forensic Medical Examination, regional bureaus, and medical files related to non-fatal poisoning incidents with psychotropic and narcotic substances were reviewed.

Among the 422 survivors of acute poisoning with these substances, 348 were male and 74 were female. In the group of 191 fatalities caused by acute poisoning with narcotics and psychotropic compounds, 188 were male and 3 were female.

Diagram 1 illustrates the gender distribution of the victims.

As shown in the diagram, males predominated among both non-fatal and fatal poisoning cases. This trend likely reflects a higher propensity among men to engage in hazardous behaviors and a comparatively weaker instinct for self-preservation than that observed in women.

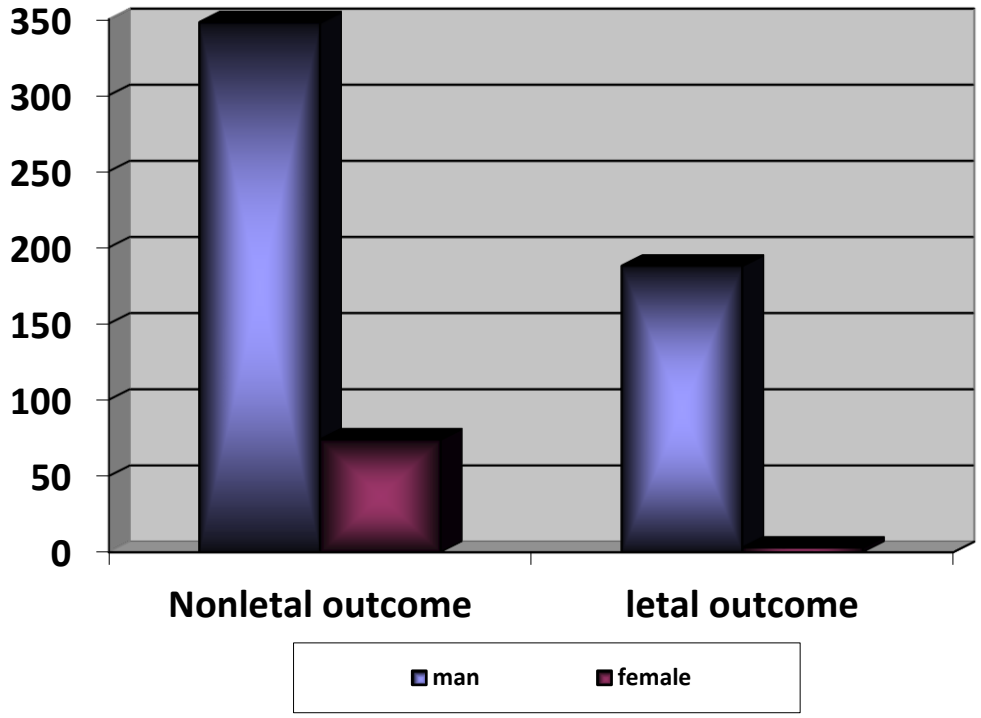


Figure. 1. Distribution of victims by sex

Examining the age demographics of those affected by poisoning revealed a notable difference between non-fatal and fatal outcomes. Individuals experiencing non-fatal poisonings had an average age of 28.2 years (with a standard deviation of

0.5), while those who succumbed to poisoning were, on average, 32.6 years old (with a standard deviation of 1.7). These findings underscore that poisoning from drugs and psychotropic substances disproportionately impacts individuals in their youth and prime working years. This observation highlights the problem's dual nature, extending beyond forensic concerns to encompass significant social implications.

The clinical investigation involved a review of patient records for individuals admitted due to acute poisoning from drugs or psychotropic substances. Within the 422 instances of non-fatal poisoning, 273 were attributed to psychotropic substances, and 149 to drug-related causes. Among the 191 fatal poisonings, psychotropic substances were implicated in 125 cases, and drugs in 66. A visual representation of the distribution of poisonings by toxic substances is presented in the accompanying figure.

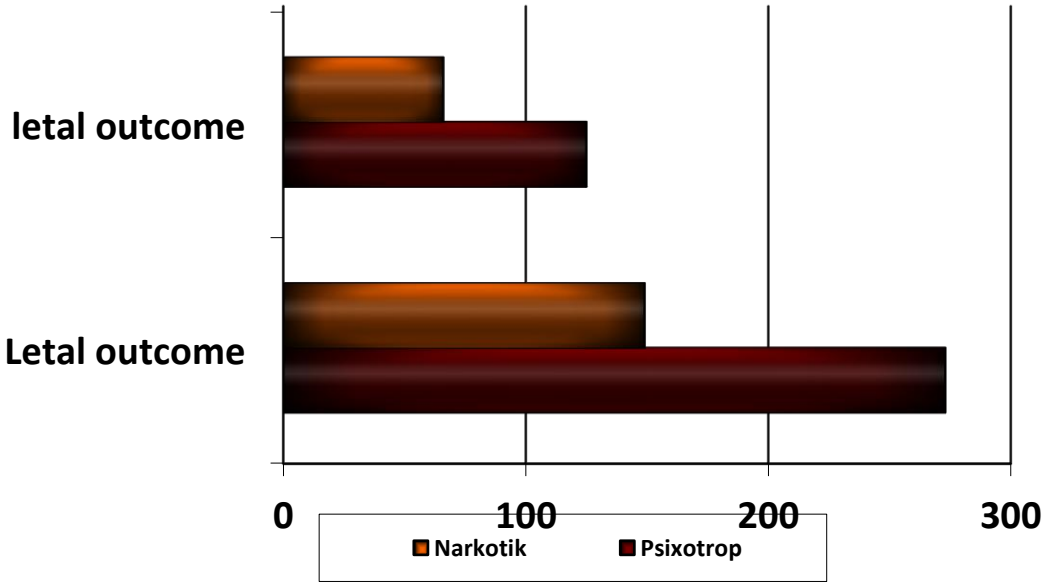


Figure 2. Occurrence of toxic substance poisoning

The prevalence of fatalities among victims exposed to various toxic agents indicates that the primary cause of death is often attributed to poisoning by psychotropic substances.

Our investigation involved a review of archival data from the Tashkent City Bureau of Forensic Medical Examination, encompassing:

An examination of 60 instances of fatal drug poisoning.

An analysis of 63 medical records pertaining to patients hospitalized with acute poisoning.

Forensic investigations in this domain typically involve establishing several key factors:

• Identification of a submitted substance as a narcotic or psychotropic agent, specifying its type and quantifying its mass.

• Detection of narcotic or psychoactive substances within the submitted research material, including any residual traces, and their specific identification.

• Confirmation and identification of narcotic substances present in biological samples.

Therefore, a forensic medical expert conducting an examination in cases of acute poisoning is tasked with addressing these critical inquiries:

Objects of expert document analysis: examination reports at the location of the body, decisions on the appointment of a forensic medical examination, death certificates, outpatient records, stationary records, transport service dispatch sheets of the deceased and the deceased.

In all observations of drug and psychotropic substance intoxication, this was confirmed by the case materials, clinical manifestations, intravital quantitative determination of these substances and their metabolites in blood and urine.

The following main studies were conducted using physicochemical analysis methods:

Microscopic examination

IR spectroscopy with full internal reflection additive

Chromatography-mass spectrometry (GC-MS)

High-performance liquid chromatography with a mass spectrometric detector (HPLC-MS) allows for quick and accurate resolution of problems in determining the type of poison.

Computerized gas-liquid chromatography with mass spectrometric determination (GC-MS analysis) was carried out. The method is based on the ionization of atoms and molecules of a substance by removing or eliminating electrons with the formation of positive ions and determining the value of the mass-charge ratio. Compared to other methods, the reliability of identification is significantly increased due to the use of the specific property of the substance, based on mass spectrum indicators in conjunction with the retention time obtained from the chromatographic process. Since the mass spectrum reflects the structure of the molecule, a detailed study of it allows one to draw conclusions about the structure and formula of the analyzed substance. The GC-MS method can be used to examine medications in biological fluids and objects (blood, urine). The use of the presented GC-MS method allows for the identification of many practically significant compounds in various objects, including powders, plant materials, and biofluids, without the use of standard samples. For non-standard identification, search algorithms are used in the spectral library, and individual storage indices of the target components are also taken into account. GC-MS methods provide high selectivity and sensitivity. These systems facilitate the attainment of low detection limits and robust reliability when identifying and verifying numerous target compounds across diverse biological samples. This holds true even within intricate matrices, where routine analysis at low concentration levels is performed.

In conjunction with toxicometric investigations, clinical observations were scrutinized and integrated into the comprehensive database. These included metrics related to central nervous system activity (varying degrees of consciousness depression), respiratory ailments (compromised external respiration, such as bradypnea, tachypnea, or apnea), cardiovascular and vascular system dysfunctions (blood pressure fluctuations, heart rate variations), neurological manifestations (alterations in pupillary dilation and responsiveness), and various emergent complications (e.g., pulmonary edema, progression to coma).

Furthermore, "Methodological recommendations: Method for calculating quantitative indicators of drug poisoning of the liver using the morphometric study method" were formulated and disseminated. The application of thermal desorption

surface ionization spectroscopy (TDS) led to the development of an efficacious technique for quantifying morphine concentrations in blood, post-mortem urine, and in the blood and urine of living individuals.

This research culminated in the establishment of a comprehensive data repository, detailing key toxicity metrics for illicit and controlled substances. This database encompasses their clinical manifestations, pathological changes, laboratory markers, and pharmacokinetic profiles. Furthermore, the study yielded objective, quantifiable criteria for diagnosing and assessing the severity of chemical injury in both acute and chronic intoxications involving these substances.

A novel "Method for extracting parent drug compounds from aqueous solutions" was devised, assigned application registration number IAP 20150297. Concurrently, methodological guidelines titled "Method for calculating quantitative indicators of drug-induced liver damage using morphometric analysis in acute drug poisoning" were developed and disseminated. Dose-response probit models were constructed, enabling a quantitative evaluation of mortality risk across the full spectrum of morphine concentrations in blood.

The investigation elucidated the patterns of poisoning by narcotic and psychotropic agents and characterized their effects in fatal outcomes. A series of predictive nomograms were generated, facilitating prompt and precise risk assessment for fatalities associated with these toxins. In post-mortem examinations, these tools allow for the determination of the exact cause of death based on the initial stage of demise. Moreover, by analyzing the presence of these substances in environmental samples and deceased tissues, it's possible to reconstruct the clinical and morphological presentation at any point during the poisoning process and gauge the extent of chemical damage in non-fatal cases.

The Patent Office issued a favorable ruling for the invention, "Method for Separating Essential Medicines from an Aquatic Environment." Clinical and histopathological analyses revealed that the systemic toxicity of opiates primarily targets the central nervous system, suppressing vasomotor and respiratory centers. This leads to widespread microcirculatory and circulatory disturbances, impaired tissue metabolism, and ultimately, functional decompensation of organs and the

entire organism. For the toxicometric assessments, a specialized HUMAL YZER Promus biochemical analyzer (model 18200) was employed.

CHAPTER I. ANALYSIS AND EVALUATION OF CLINICAL AND TOXICOLOGICAL DATA ON NON-FATAL POISONING BY OPIATE AND PSYCHOTROPIC DRUGS, EPIDEMIOLOGY OF POISONING CASES.

The research focused on clinical and toxicological (toxicometric) information, specifically concerning the toxicity parameters of drugs like morphine and other opiates, alongside the clinical indicators of non-fatal intoxications involving drugs and psychotropic substances. To gain a deeper understanding, the study involved toxicological, clinical-anatomical, thanatological, and morphological examinations of samples from acute poisonings with these substances.

Clinical data were gathered by reviewing the medical records of patients admitted to hospitals due to acute poisoning from narcotic drugs, psychotropic substances, or a combination thereof.

A comprehensive review was conducted on 348 sets of medical documents pertaining to non-fatal poisonings caused by psychotropic and narcotic substances.

In every instance, the poisoning by the aforementioned substances was corroborated by observable clinical symptoms and the quantitative detection of these substances in both blood and urine samples.

The cases of drug and psychotropic substance intoxication chosen for the analysis and evaluation of clinical and toxicological (toxicometric) data were selected randomly. The sole selection criterion was the quantitative presence of these substances in blood and urine, which suggests that the data accurately represent typical drug and psychotropic substance intoxication scenarios.

Table 1 details the findings from the analysis of toxic substances identified in non-fatal psychotropic substance poisoning cases, while Figure 1 illustrates the frequency of such poisoning incidents.

Table 1

Distribution of non-fatal cases of intoxication by toxic substances (n - number of cases)

Toxic substance	Uncombined (n-156) Uncombined (n-156)	Uncombined (n-156) Uncombined (n-156)
Diphenhydramine	**104**	**40**
Amitriptyline	**23**	**–**
Carbamazepine	**4**	**–**
Azoleptol	**3**	**–**
Benzodiazepine derivatives	**5**	**–**
Diobinol	**1**	**–**
Phenocypam	**2**	**–**
Barbiturates	**6**	**–**
Diclofilin	**2**	**–**
Sonnate	**3**	**5**
Phenothiazine	**3**	**–**

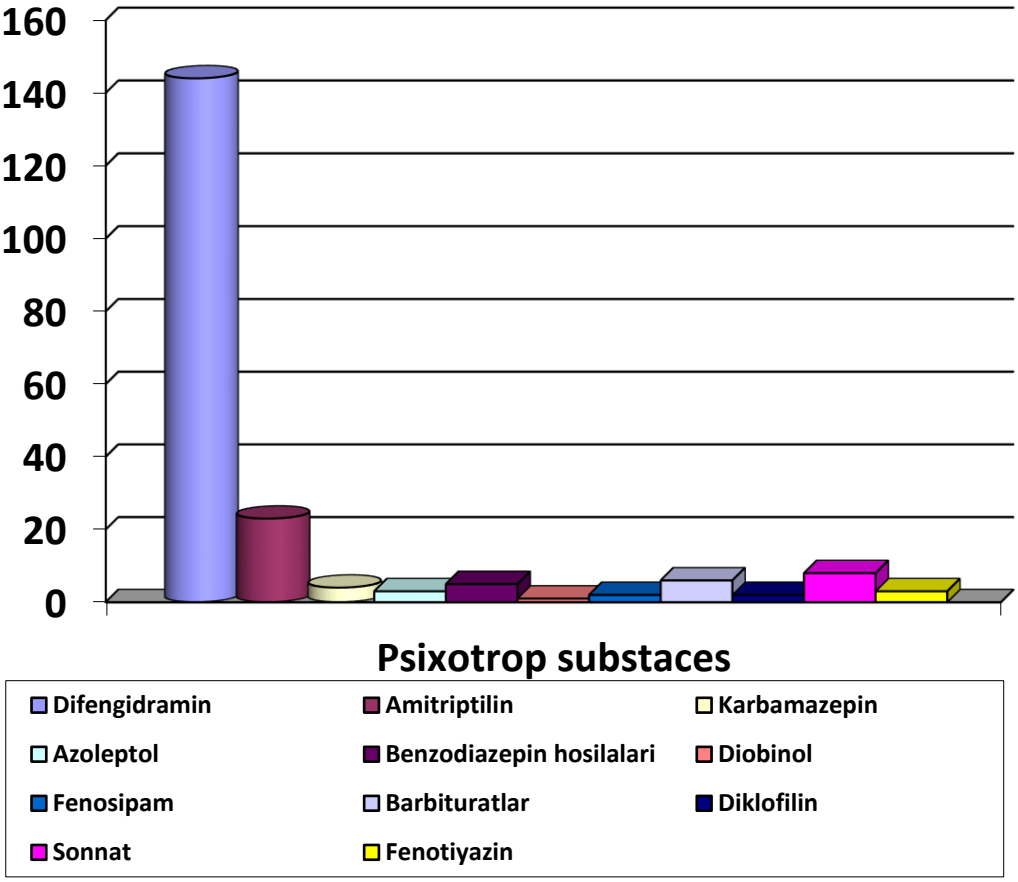


Figure. 1. Non-fatal cases of intoxication by psychotropic drugs

A review of non-fatal poisonings involving psychotropic substances revealed a higher incidence of diphenhydramine intoxication. Notably, diphenhydramine emerged as the primary agent in both combined poisonings with other psychotropics and in instances where psychotropic and narcotic substances were co-ingested. Table 2 details the distribution of these non-fatal combined intoxications, illustrating the frequency of such co-ingestions.

Table 2

Distribution of cases of non-fatal combined intoxication with psychotropic and narcotic substances by toxic substances (n - number of cases)

Combined toxic substance	Dimedrol (n) Sonnate (n)	Dimedrol (n) Sonnate (n)
Opiates 34. 5.	34	5

of which:		
Morphine 23 5	23	5
Heroin 3	3	–
Codeine 2	2	–
Phenozipam 4	4	–
Amitriptyline 2	2	–

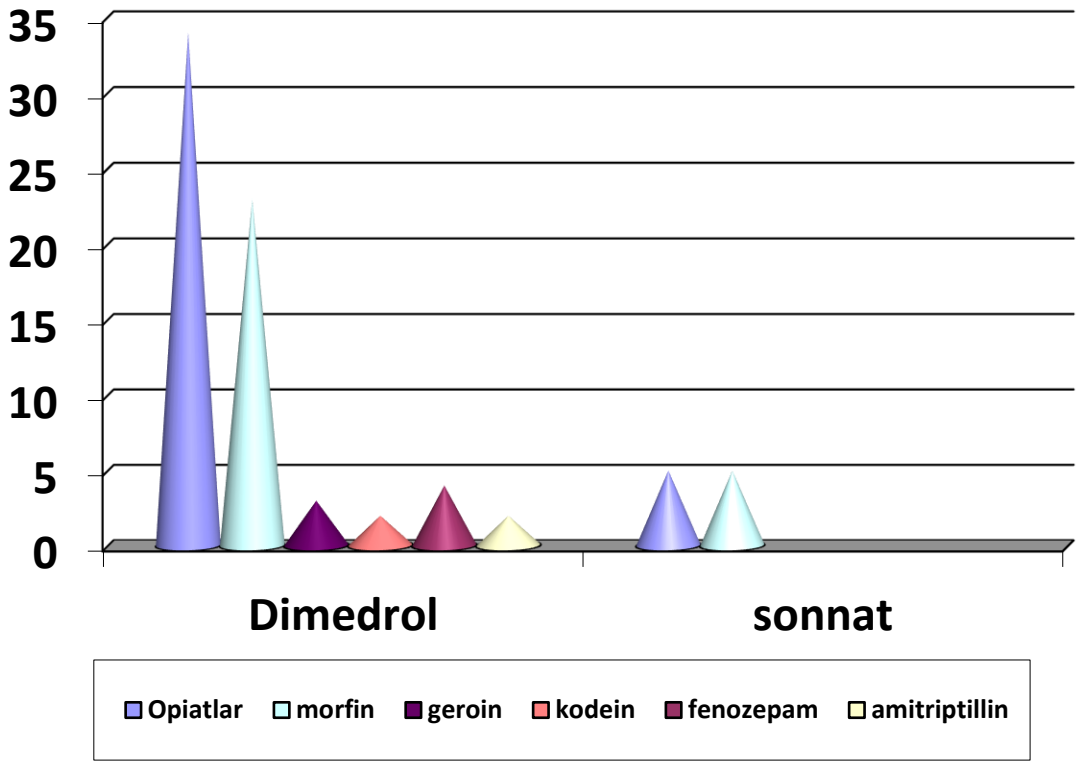


Figure 2. Frequency of non-fatal cases of combined intoxication with psychotropic and narcotic substances.

Our examination of the non-fatal outcomes stemming from instances of polysubstance intoxication involving psychotropic and narcotic agents revealed opiates as the co-toxicant in the majority of cases. Only six instances involved combined intoxication with two psychotropic substances. Furthermore, we

investigated 141 cases of non-fatal drug poisonings. The findings regarding the toxic substances identified in these non-fatal drug poisoning incidents are detailed in Table 3, while the prevalence of such cases is illustrated in Figure 3.

Table 3

Distribution of cases of non-fatal drug poisoning with toxic substances (n - number of cases)

Toxic substance	Uncombined (n) Combined (n)	Uncombined (n) Combined (n)
Opiates	51	57
(108 cases in total)		-
of which:		-
Morphine	35	57
Heroin	11	-
Codeine 5 -	5	-
Cannabinoids (hemp)	31	-
Tramadol	2	-

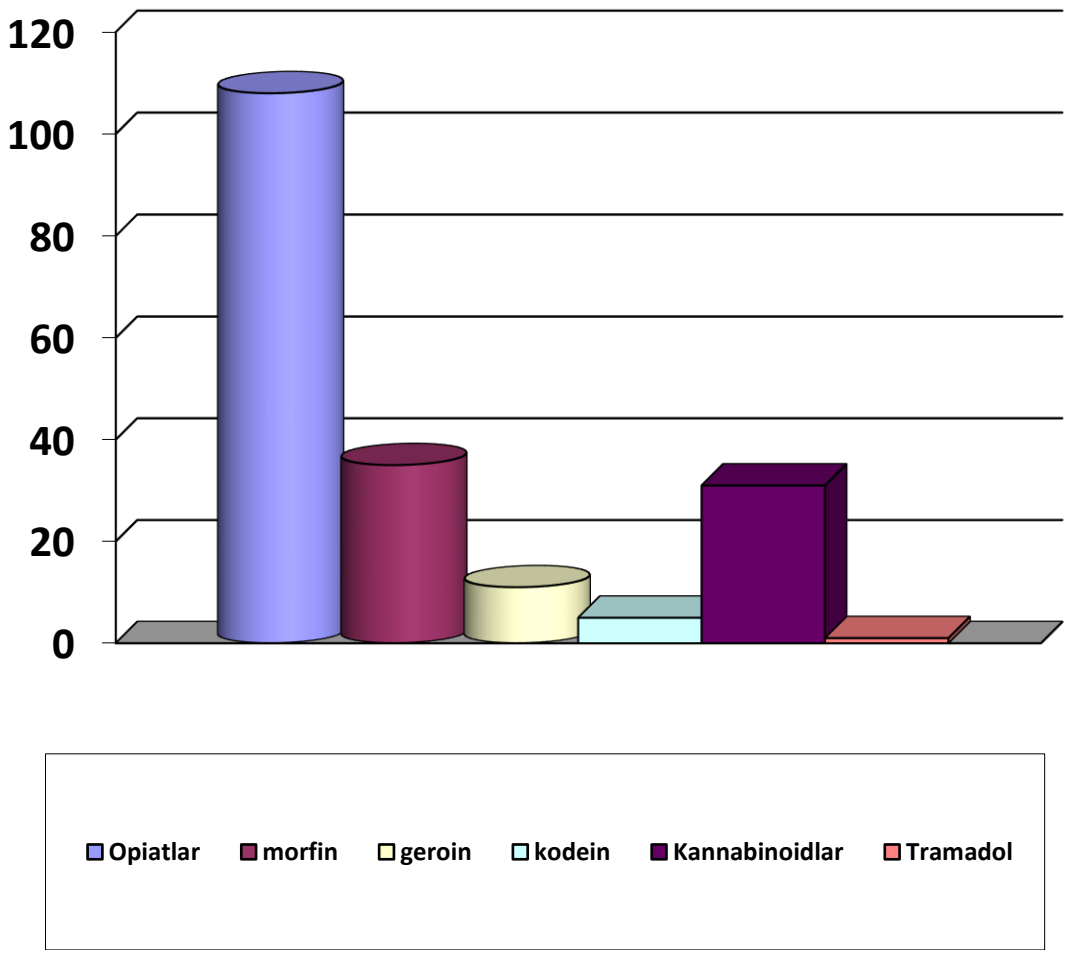


Figure. 3. Cases of non-fatal drug poisoning

The provided table data reveals that opiate poisoning, specifically from the alkaloid group (e.g., morphine), is the most prevalent type among all non-fatal drug intoxications. Morphine alone accounted for 108 cases, with 92 attributed to morphine, 11 to heroin, and 5 to codeine. While opiates were the sole detected substance in 64 cases, 53 cases involved additional substances like diphenhydramine, papaverine, and thebaine. Cannabinoid poisoning also frequently appeared in our observations. Further analysis of combined intoxications showed diphenhydramine present alongside opiates in 38 cases. Additionally, co-occurrence of multiple opioids was observed, with morphine and heroin detected together in 10 cases, and morphine and codeine in 9 cases.

Our current research phase involved a toxicometric evaluation of morphine. The significant challenge in identifying drugs and psychotropic substances in post-mortem samples, particularly when no physical signs or prior drug use history are available, demands the use of highly sensitive forensic chemical analysis tools. These advanced instruments are crucial not only for confirming the presence of a drug in cadaveric material but also for quantifying its amount. Consequently, toxicometric investigations of morphine, employing the sensitive surface ionization indicator PII-N-S "Iskovich-1," are designed to detect minute quantities of drugs and other substances in biological samples (urine, blood, and cadaveric material) from individuals who have consumed them. This detection is achieved through thermal desorption surface ionization spectroscopy (TDS). The development of this indicator is credited to the Research Institute of Electronics of the Academy of Sciences of the Republic of Uzbekistan, under U.A. Arifov (now the Institute of Ion-Plasma and Laser Technologies of the Academy of Sciences of the Republic of Uzbekistan).

The thermal desorption surface ionization indicator (TDII) functions by precisely controlling the temperature to evaporate molecules of the substances under investigation. Subsequently, the ions generated during this desorption process are recorded, yielding thermal desorption surface ionization (TDPI) spectra.

This instrument was selected due to its critical attributes for our research. Notably, its exceptional sensitivity enables the detection of minute quantities of drugs within biological matrices (e.g., 10-10 g of morphine), significantly surpassing the capabilities of thin-layer chromatography (TLC). The integration of the Iskovich-1 system has facilitated our approach to analyzing substantial volumes of biological samples. Furthermore, this unique device enhances research quality, as it forms an integral part of comprehensive laboratory investigations when combined with TLC and colorimetric assays. Its deployment is also economically advantageous, delivering results more rapidly than alternative chemical methodologies. The updated DRUGGY-4 software further extends its utility by enabling quantitative analysis.

From 2006 to 2014, forensic chemistry units within the Bureau of Forensic Medical Examination, under the Tashkent City Health Department, conducted extensive validation of research findings related to the determination of drug TDPI spectra. This work was overseen by M.M. Ibragimova, a Candidate of Medical Sciences affiliated with the Main Bureau of the Ministry of Health of the Republic of Uzbekistan. The TDPIS system functions by employing controlled thermal evaporation (desorption) of the target molecules, which are subsequently detected by a surface ionization sensor as they pass through the air stream (see Figure 4).

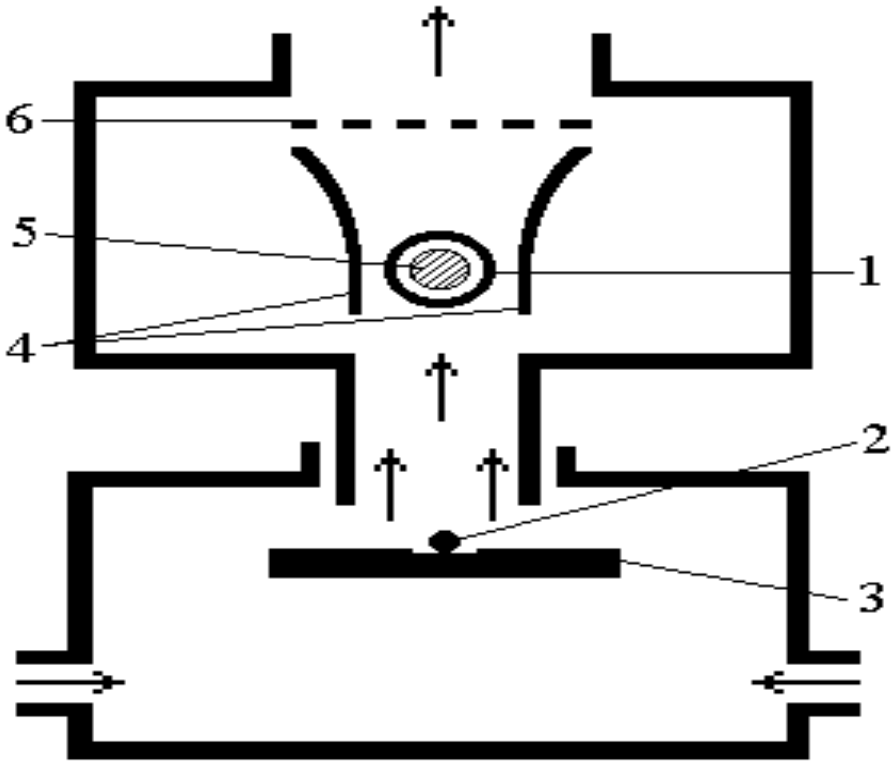


Figure. Diagram of a thermal desorption surface ionization spectrometer: 1 - emitter; 2 - sample for analysis; 3 - evaporator; 4 - focus electrodes; 5 - heater; 6 - ion collector.

A microquantity of the analyzed sample is applied to the surface of the evaporator, through which an electric current is passed and heated in a certain temperature range in a certain mode of time variation T and T (t). Evaporated molecules enter the FID with an airflow, where they are ionized (air and solvent molecules are not

ionized by PI) and the I (t) dependence of the ion flow is recorded synchronously with the T (t) dependence.

The registered flow is proportional to the number of ionized molecules reaching the emitter surface, the latter is proportional to the number of molecules evaporated (desorbed) from the surface of the evaporation apparatus. Therefore, the dependence of the ion flow on the evaporator's T (thermal desorption (evaporation) spectrum) is specific to each analyte and reflects the analyte and its quantity in terms of Tmax and the field under the spectrum.

TDPIS research is carried out under the following instrumental conditions: emitter temperature 380-4200C, emitter flow voltage 400 V, evaporator temperature from room temperature to 5000C, scanning, spectra are recorded on the monitor, and the flow value varies within the range. 10-11 ÷ 10-7 A.

The spectrometer is connected to a personal computer, and from the created data bank of thermal desorption spectra of drugs and other drugs, using calibration graphs of each test substance, using the created programs Druggy-1A and Druggy-4A, you can identify the analyzer and determine its concentration in the test sample.

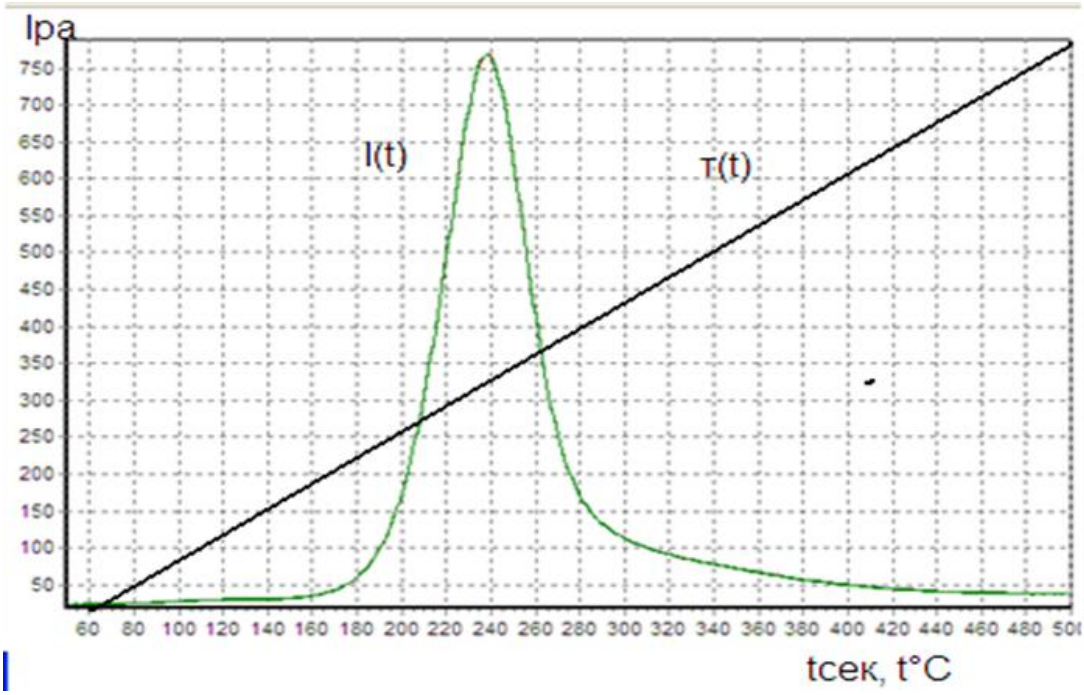


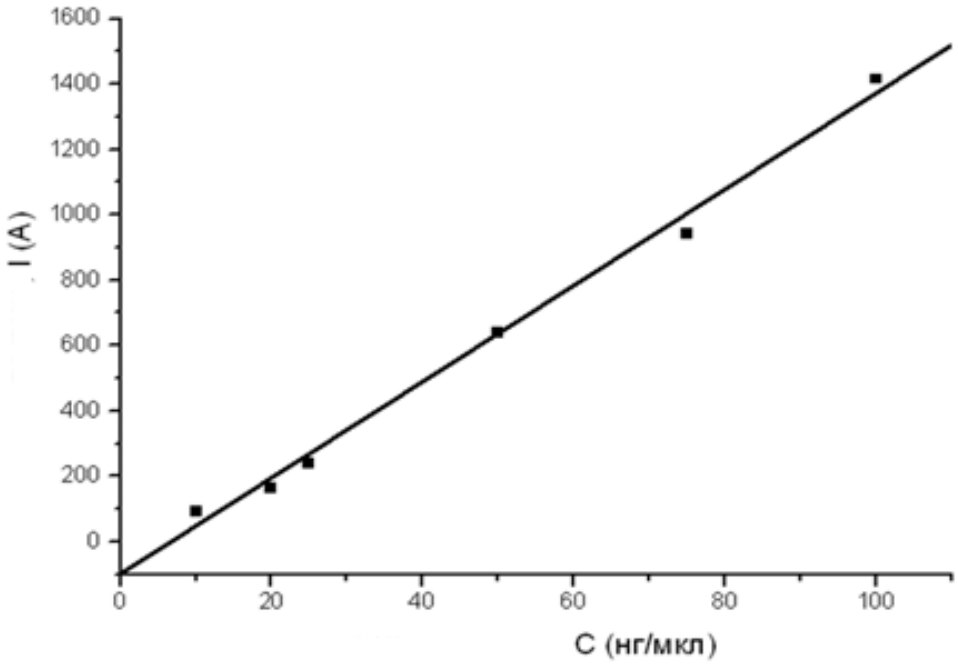
Figure 5. Calibration table

When working with this device, we applied the appropriate research methodology. Ethyl alcohol was used to measure the TDPI spectra, since the methodological recommendations for the operation of the device recommend the use of this solvent.

In the study of pure substances, 10 mg of pure substance of the tested preparation was dissolved in 10 ml of ethanol. From this amount, 1-2 μl were measured with a microspray (precise amounts, since these results were subsequently used for the quantitative determination of the studied preparation), applied to the cylindrical recess of the evaporator tape device and subjected to thermal desorption spectroscopy.

The obtained TDPI spectra were found to be effective in the current range of 100-2000 A. If the spectra were outside this range, then a dilution of ethanol solutions of the studied drugs was carried out.

At this stage of the study, the morphine content was determined using the TDPIS method. For this purpose, a calibration graph was constructed using the thermal desorption spectra of morphine in ethanol at different concentrations: 10 ng, 20 ng, 25 ng, 75 ng, 100 ng (Fig. 6).



current strength **concentrasion**

Figure. 6. Calibration graph for determining morphine content.

along the abscissa axis - concentration of the test solution (C), ng/μl;
along the ordinate - the magnitude of the current (I) in the investigated solution at Tmax, A.
The amount of morphine isolated from the biological material is calculated by the formula:

$$X = \frac{C \times V_1 \times V_3 \times 100}{V_2 \times n \times 1000}$$

Here:

X - amount of morphine isolated from the biological object, mg%;

n - weighed part of the biological object (sample taken), ml (g);

V1 - initial chloroform extract, ml;

V2 - volume taken from V1 for quantitative determination, ml;

V3 - volume of ethanol taken to dissolve the dry residue (V1 after evaporation) during the test of the sample for PII-N-S, ml.

C - morphine concentration found from the calibration graph, μg/ml.

The morphine spectra obtained as a result of calculating the quantitative determination of morphine isolated from the blood of a person who consumed it are shown in the figure. 7.

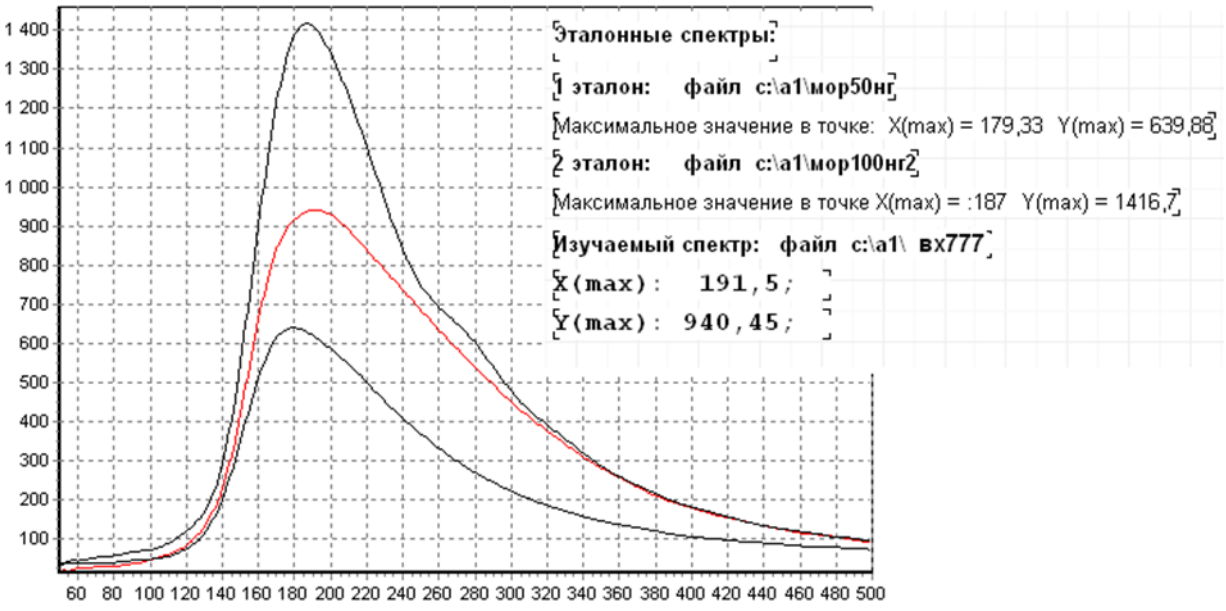


Figure 7. TDPI spectra of morphine.

along the abscissa axis - evaporator temperature (T), 0C;

along the ordinate - the magnitude of the flow (I), A.

The figure above shows that the current strength of the studied spectrum is 940.45 A. The concentration in the test sample in our case was determined by a graph of 75 ng/ml or 75 μg/ml.

The amount of morphine in the blood is calculated by the formula:

During this scientific study, a method was developed for determining the concentration of murphine in blood, urine, and internal organs of the corpse, as well as in the blood and urine of living people. The proposed methodology includes an approximate calculation of the morphine dose taken by a person for any purpose and literature data that can be used in the practical activities of forensic experts to interpret the results of forensic chemical analysis and more reliably diagnose the presence of drugs in biomaterial.

This technique was tested on expert material (74 cases). In most cases, opiate poisoning, detected using the method we proposed, is confirmed by the case materials, clinical and morphological images.

CHAPTER II. CLINICAL AND MORPHOLOGICAL ANALYSIS OF THE FATAL RESULT IN DRUG AND PSYCHOTROPIC POISONING WITH THE IDENTIFICATION OF MORPHOLOGICAL MANIFESTATIONS LEADING TO DEATH. DETERMINATION OF MORPHOMETRIC PARAMETERS CHARACTERIZING THE STATE OF LIVER TISSUE IN ACUTE MEDICINAL INTOXICATION.

The prevalence of clinical signs of poisoning was studied in accordance with the concentration of drugs in the blood and a clinical and morphological analysis of lethal outcomes was carried out, morphological manifestations, clinical and morphological (toxicometric) data in fatal drug and drug poisoning with psychotropic substances were determined.

For this purpose, expert documents were analyzed: examination reports at the location of the body, decisions on the appointment of a forensic medical examination, death certificate forms, outpatient and inpatient records.

In all fatal poisonings, drug, psychotropic substance poisoning or combined poisoning is confirmed by case materials, clinical picture, quantitative determination of drugs or psychotropic substances and their metabolites in blood and urine, as well as subsequent determination in urine of the same victims, who were treated in the hospital where the death occurred. In all cases, total morphine (the sum of free and conjugated compounds) was determined in blood plasma and urine using the TDPIS method.

The results of the analysis of data on toxic substances identified in fatal cases of poisoning with psychotropic substances (5 cases in total) are presented in Table 4.

Table 4

Distribution of fatal cases of poisoning with psychotropic substances by toxic substances (n - number of cases)

Toxic substance	Uncombined (n) Combined (n)	Uncombined (n) Combined (n)
Dimedrol	2	2
Amitriptyline	1	–

As can be seen from the data in this table, both in cases of combined lethal poisoning with psychotropic substances and in cases of combined lethal poisoning with psychotropic and narcotic substances, the greatest number of cases occurred with diphenhydramine poisoning.

In both cases of fatal combined poisoning, diphenhydramine is combined with morphine.

In addition, we analyzed cases of poisoning with lethal drugs (a total of 28 cases).

The results of the analysis of data on toxic substances identified in cases of poisoning with lethal drugs are presented in Table 5.

Table 5

Distribution of lethal drug poisoning cases (n - number of cases)

Toxic substance	Uncombined (n) Combined (n)	Uncombined (n) Combined (n)
Opiates	4	23
of which:		
morphine	2	23
heroin	2	–
Tetrahydro-cannabinoids (anasha)	1	–

As can be seen from the data in this table, among all fatal cases of drug poisoning, poisoning with opiates - poisons of the alkaloid group - occurs most often, among which, as in uncomplicated poisoning, morphine and heroin also predominate, in all cases morphine was detected. Fatal tetrahydrocannabinoid poisoning was detected in only one case.

The results of a more detailed analysis of the distribution of cases of combined poisoning with toxic substances are presented in Table 6.

Table 6

Distribution of cases of combined drug and psychotropic substance poisoning by toxic substances (n - number of cases)

Combined toxic substance Morphine (n)	**Combined toxic substance Morphine (n)**

Codeine	**6**
Thebaine	9
Papaverine	6
Dimedrol	2

Analysis of the distribution of fatal cases of combined intoxication with narcotic drugs and psychotropic substances showed that the most frequent cases were combined intoxication with two types of opiates (91.3%). Combined poisoning with morphine and diphenhydramine was detected only in 2 cases.

Forensic medical examination of fatal drug and psychotropic substance poisonings includes the following stages.

1. Analysis of expert documentation: protocols of examination at the place of discovery of the corpse, decisions on the appointment of a forensic medical examination, death certificate forms, outpatient cards, stationary cards, certificates of transportation of the deceased and the deceased.

- 33 sets of expert documents with medical histories were analyzed.

2. Macroscopic examination of the deceased:

- 16 macroscopic signs were studied in each case.

3. Microscopic examination of fragments of internal organs was carried out in all 33 cases:

- in each case, from 9 to 14 histological preparations were studied (a total of more than 100).

4. Ultrastructural examination of the heart, brain, and lung lobes:

- More than 100 samples were studied.

5. In all cases, the results of general forensic chemical and toxicological studies were analyzed:

- in 33 cases in the blood, urine, and internal organs (liver, kidneys, stomach) of the deceased;

- In 348 cases - in the blood and urine of the recovered.

6. Statistical research methods were also used in the study of the obtained data:

- grouping and generalization of indicators;
- search statistics (definition, determination of the frequency of occurrence of averages and intervals;

Epidemiological analysis of fatal poisonings from opiates and psychotropic substances showed that the development of objective and scientifically based approaches to the modern diagnosis and assessment of fatal poisonings from narcotic drugs and psychotropic substances requires the study of the structure of these pathologies.

In the composition of forensic medical examination materials, fatal opiate poisonings, due to their social, economic, and forensic significance, undoubtedly occupy one of the most important places.

The largest number of deaths from poisoning with narcotic drugs and psychotropic substances were men (93.9% (31), compared to them, the incidence of these poisonings in women is significantly lower than in men - 6.1% (2).

Mortality from drug and psychotropic substance poisoning is most often observed in young people aged 21 to 30. This group, which corresponds to the most working and active age, accounts for 66.7% of deaths from these poisonings.

Analysis of forensic medical examination findings shows that 24 (72.7%) of the deceased died from direct intoxication as a result of early poisoning complications (acute respiratory and cardiovascular failure, toxic coma). In 9 observations (27.3%), the course of acute opiate intoxication was complicated by the appearance of a new pathological process (pneumonia, encephalopathy, sepsis), which was considered a complication of the underlying disease, influencing the onset of mortality, and at the same time associated with the decompensation of somatic pathology caused by prolonged drug use.

We identified the direct toxic effects of drugs and psychotropic substances, such as paralysis of the respiratory center (acute respiratory failure) and paralysis of the vasomotor center (acute cardiovascular failure).

Among the initial complications, the most common are collapse (acute cardiovascular insufficiency), toxic pulmonary edema (acute respiratory failure), and toxic coma (cerebral edema).

Among the late complications, the most common in our observations were pneumonia and encephalopathy.

Generalization of complications was manifested by exogenous intoxication with decompensation of somatic pathology, sepsis, and multiple organ manifestations.

In all the studied cases, the identified macro- and microscopic signs of the toxic effects of drugs and psychotropic substances manifested against the background of the morphological picture of damage to internal organs as a result of prolonged use of these substances.

Our clinical and morphological analysis allows us to conclude that in each specific case, the development of the pre-death period is associated with pathological processes, the interpretation of which is ambiguous due to the complexity of the developing cause-and-effect relationships.

Acute intoxication with drugs or psychotropic substances is a major disease that leads to the development of various types of terminal conditions and, as a result, various causes of death. Acute poisoning with these substances during a patient's lifetime can lead to failure of any of the three vital organs - the heart, lungs, or brain - and the development of a corresponding type of terminal condition caused by the direct toxic effects of drugs or psychotropic substances.

Morphological, morphometric, and histomorphological analyses of liver components were conducted in drug poisoning in combination with viral hepatitis.

For this purpose, liver tissue preparations obtained from non-drug users (who administered parenteral drugs) and those who died from mechanical injuries (97 cases) were compared. In each preparation, parameters characterizing all the main micro-structures of the liver were measured under normal and pathological conditions.

Liver lobules were fixed in a 10% solution of neutral formaldehyde for 48 hours, after washing in running water for 2-4 hours, dehydration was carried out in

alcohols of increasing concentration and chloroform, then they were impregnated with kerosene wax. Histological sections 5-8 μm thick were made from kerosene blocks and stained using the following histological and histochemical methods: for general morphology with hematoxylin and eosin; for determining mucopolysaccharides and glycogen by the PAS reaction method; Determination of collagen fibers using the Van Ginzon method.

CHAPTER III. ANALYSIS OF THE PURPOSE OF THE ESTABLISHED QUANTITATIVE CRITERIA FOR DIAGNOSIS IN ACUTE AND CHRONIC INTOXICATIONS WITH DRUG SUBSTANCES AND PSYCHOTROPIC SUBSTANCES AND THE SEVERITY OF CHEMICAL INJURY.

Analysis of the collected materials was carried out: medical history, expert opinions, results of forensic chemical studies of blood and urine of victims of acute drug poisoning, to determine the risk of death depending on the concentration of morphine in the blood. In all observations, opiate poisoning was confirmed by the materials of the study, the clinical picture of intoxication, intravital quantitative determination of opiates and their metabolites in blood and urine. The purpose of the study was to determine the results of acute opiate poisoning in all ranges of concentrations of their metabolites, determined during toxicological studies of the victims. To obtain the necessary data, according to a forensic chemical study, we established the initial level (in SI units - mcg/ml) of morphine, the main metabolite of opiates, in the blood. We constructed probit plots of "toxin concentration - effect" (Fig. 10). The method has found wide application in experimental and clinical toxicology.

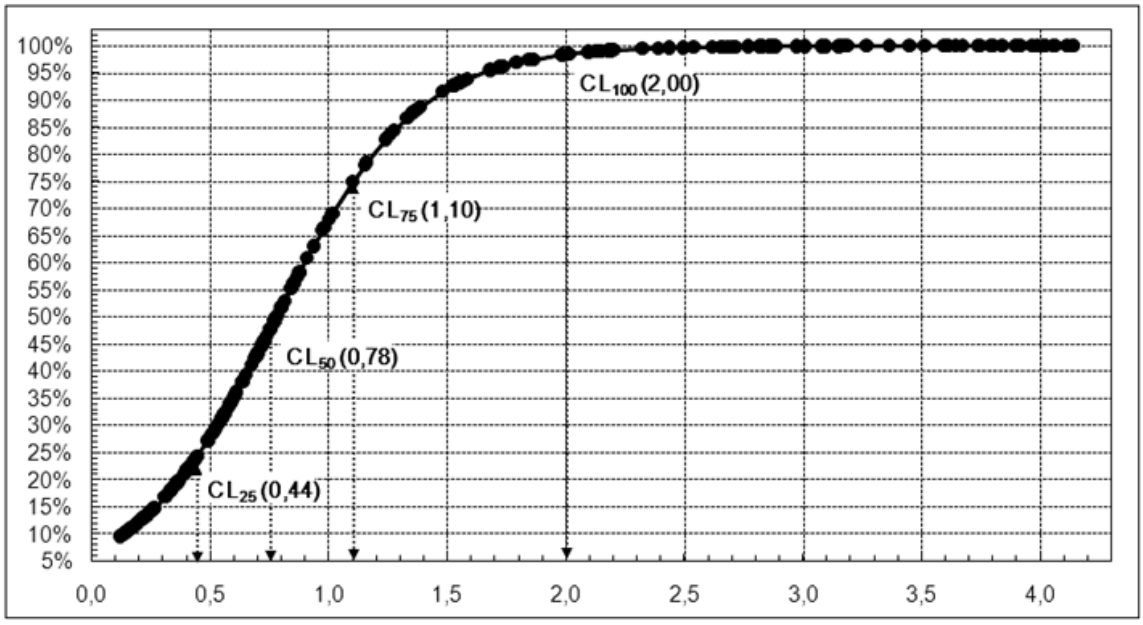


Fig.10. Probit graph of the dependence of the risk of death (%) on the concentration of total morphine in blood plasma (μg/ml) "toxin concentration - effect"

Based on the obtained graphical data, the probability of death was assessed in different concentration ranges. On the abscissa of the graph, we determined the coordinate point corresponding to the morphine level in the blood and drew a perpendicular to the intersection with the graph curve, then continued it with a left-parallel (horizontal) line until it intersected with the ordinate axis. The intersection point of this conditional line with the ordinate axis corresponded to the risk of death at this level of morphine concentration in the blood. Thus, it was possible to determine the immediate cause of death based on morphine concentration. The majority of victims (71.2%) were men aged 21-30 years (83.8%). The immediate cause of death within the first 72 hours was intoxication (34.0%). Mortality in later periods is associated with pneumonia (22.3%), myocardial dystrophy (5.6%), and sepsis (5.6%). In all cases (100%), morphine (1.5 μg/ml) was detected in the blood (n=48) during the toxicological study due to acute poisoning, and morphine was also detected in the urine of 13 victims (27%). (4, 6 μg/ml). Analysis of these graphs shows that when assessing morphine in the blood, the elevated part of the so-called "main response" curves ranges from 0.1 μg/ml to 1.4 μg/ml, in urine - up

to 0.01 μg/ml. 6 μg/ml, the result of poisoning in these concentrations is uncertain, and with an increase in the concentration of the toxic substance in the blood, the risk of death increases, i.e., the body is in a serious condition.

In addition, using this method, we conducted a comparative analysis of the risk of death for men and women, as well as by age.

Comparative analysis of the test graphs of the dependence of the risk of death in men (Fig. 11) and women (Fig. 12) on the "concentration of the poison - effect" on the total concentration of morphine in the blood showed that mortality from opiate poisoning in women is lower than in men.

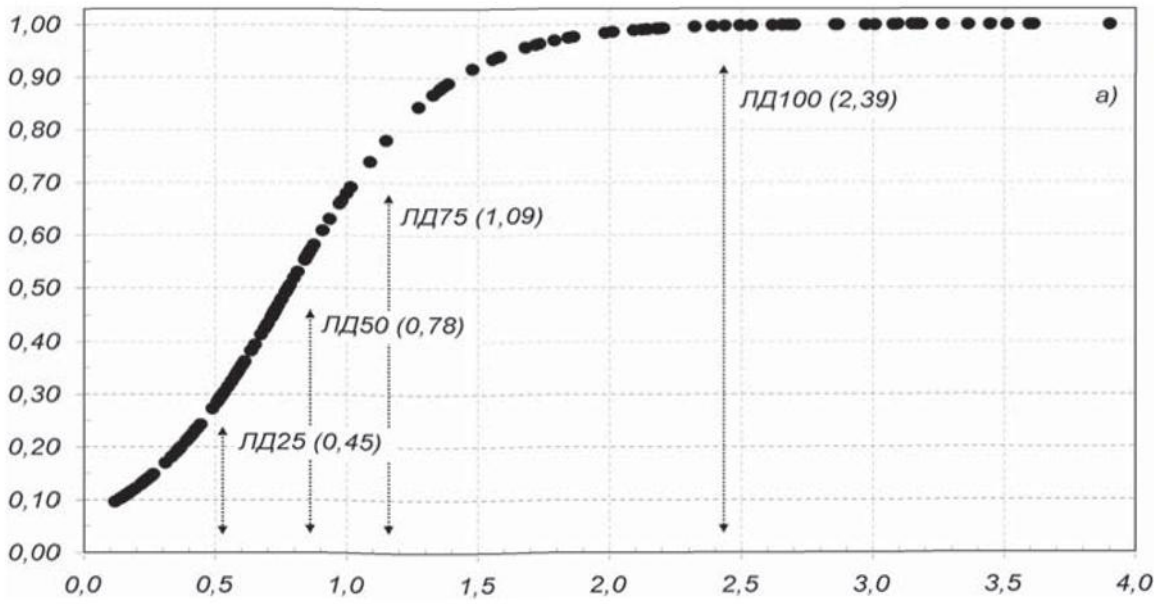


Figure 11. Probit graph of the dependence of the risk of death (%) in men on the concentration of total morphine in blood plasma (μg/ml) depending on the "toxin concentration - effect."

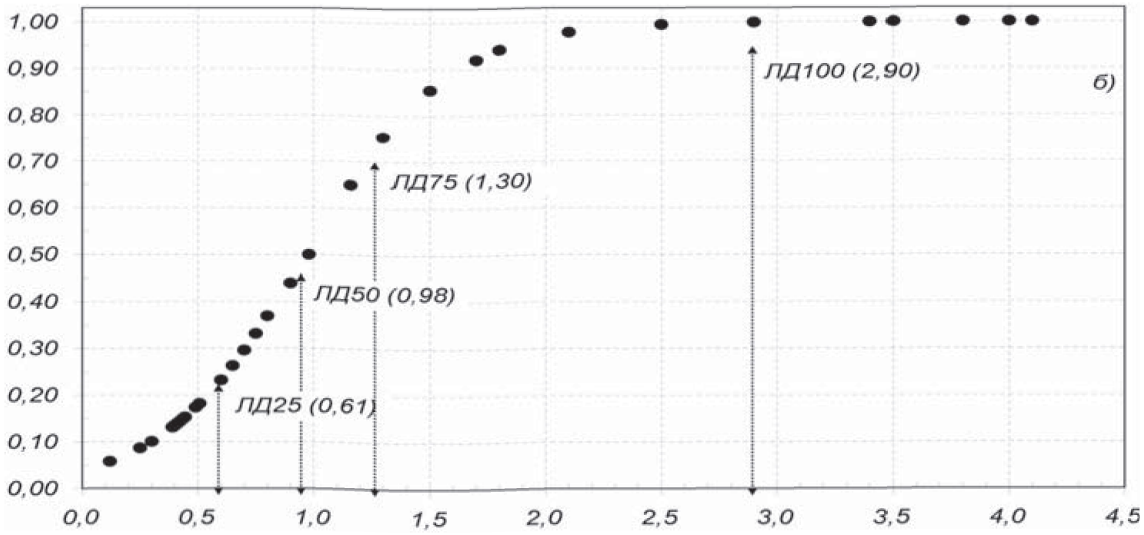


Figure 12. Probit graph of the dependence of the risk of death (%) in women on the concentration of total morphine in blood plasma (μg/ml) "toxin concentration - effect"

The concentration range was almost the same in both men and women, but, as the probit sections showed, the estimated risk of death in men is significantly higher. These graphs show that the curve of the graph is more shifted to the left in males.

In addition, they found that the critical concentration of morphine (CL50) in the blood of women was 0.98 μg/ml, while in the blood of men, the lethal concentration was significantly lower and amounted to 0.78 μg/ml. The results of a comparative analysis of the test graphs of the dependence of the risk of death on the concentration of total morphine in blood plasma showed that the female body is more resistant to the effects of opiates in the zone of high concentrations, however, as the degree of chemical damage increases, gender differences in survival are smoothed out.

The processes of tissue development, maturation, and differentiation, as well as the age-related characteristics of the morphology, physiology, and biochemistry of organs and systems of the body, influence the body's sensitivity to toxic substances and the permeability of blood vessels of tissues. Histochemical barriers, the functions of the nervous, endocrine, and immune systems, and other indicators

significantly change the nature of the organisms depending on their age, we conducted a comparative analysis of the probit graphs of the dependence of the "toxin concentration" on the risk of death in terms of age.

Comparative analysis of the probit graphs of the dependence of the risk of death "poison concentration - effect" on the total morphine concentration in the blood in victims under 25 years of age (Fig. 13) and in victims over 25 years of age. (Fig. 14) showed a significantly higher risk of death as a result of opiate poisoning in victims under 25 years of age.

In our studies, the average morphine content in the blood of victims under 25 years of age was 0.58 μg/ml, and in the blood of victims over 25 years of age - 1.17 μg/ml. The probit plots presented here show that the toxicity of opiates in these age groups is not equivalent to the same parenteral intake of opiates into the body.

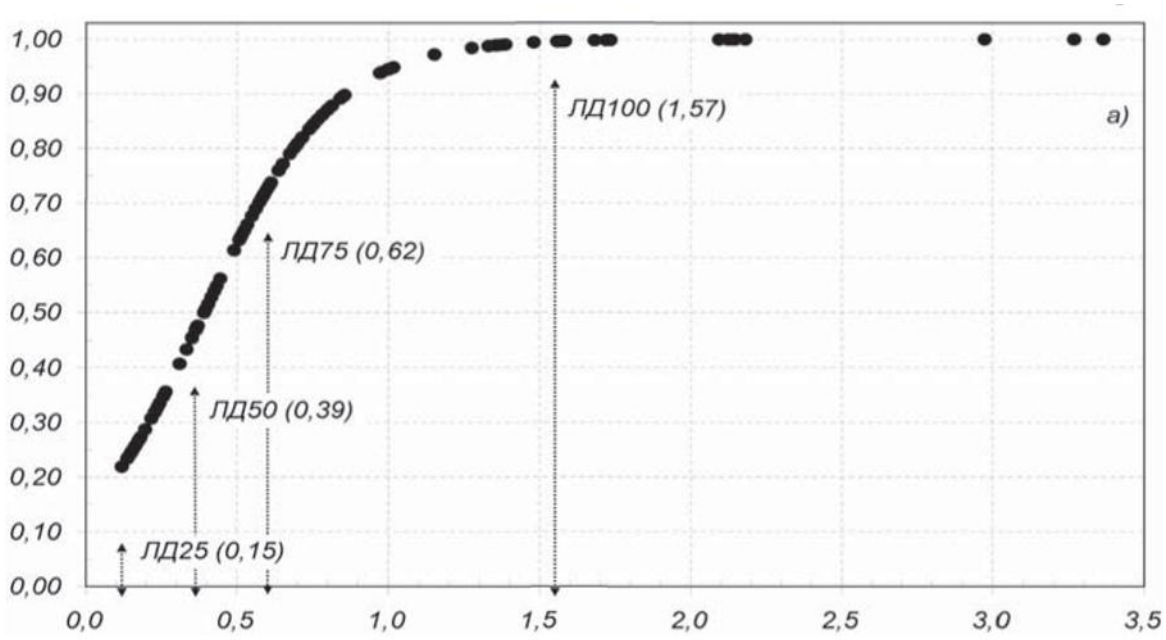


Figure 13. Probit graph of the dependence of the risk of death (%) in victims under 25 years of age on the concentration of total morphine in blood plasma (μg/ml) depending on the "poison concentration - effect."

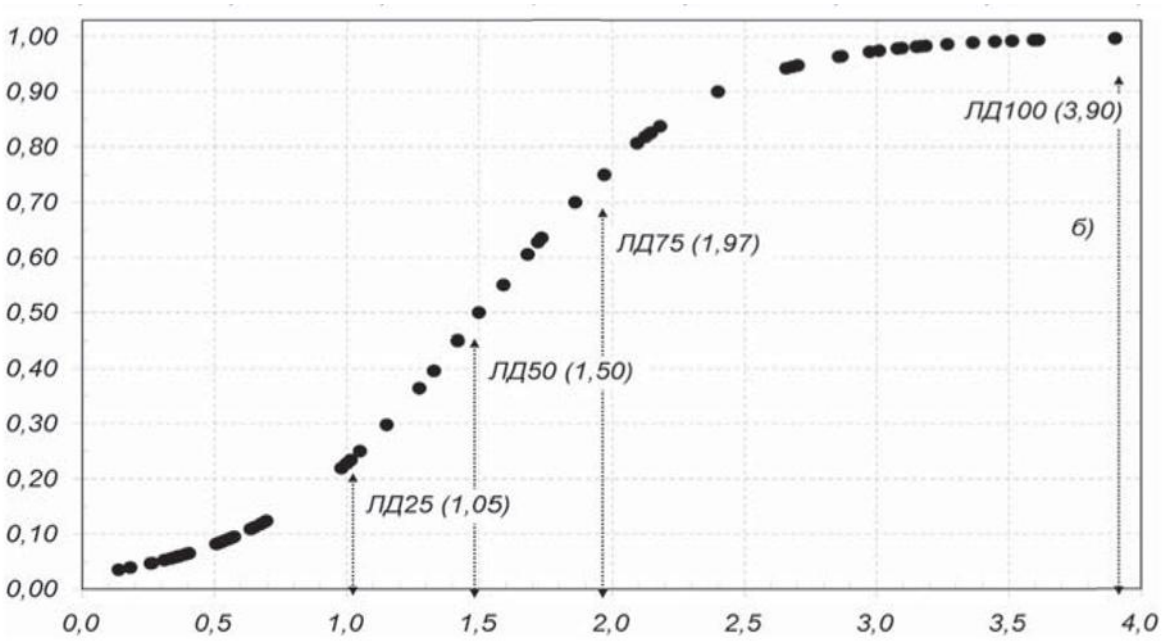


Figure 14. Probit graph of the dependence of the risk of death (%) in victims over 25 years of age on the concentration of total morphine in blood plasma (μg/ml) depending on the "poison concentration - effect."

We see the age dependence of the effect of the toxic concentration of opiate metabolites on the body. The higher the age indicators, the higher the body's resistance. For victims over 25 years of age, the morphine level in the blood of 0.5 μg/ml is significantly lower than even the CL25 dose, while the risk of death is insignificant and approaches this level for victims under 25 years of age. CL25 dose corresponding to the critical level. Moreover, in the age group under 25 years, the probit curve shifts significantly to the left, indicating a significantly higher risk of death for this group in a narrow range of morphine concentration in the blood (CL25 = 0.15, CL50 = 0.62, CL100 = 1.57), while in the age group over 25 years, the outcome of poisoning is often uncertain, with a critical level of 3.9, corresponding to the dose of CL100.

Therefore, in our opinion, positive forensic chemical examination results cannot be clearly interpreted as evidence of fatal opiate poisoning, especially if they are detected and their metabolites are detected only in urine, even if their quantity is determined. Thus, the developed probit plots of the "toxin concentration

- effect" relationship allow for a quantitative assessment of the risk of death in all ranges of morphine concentrations in the blood.

Calculation of the maximum and minimum ranges of morphine concentration in the blood (CL0 - CL25, CL50 - CL75, CL75 - CL100) allowed us to determine the concentration ranges (M±2s), including 95.4% of the values we observed. It is assumed that the threshold concentration (CL0 - CL25), corresponding to the table we proposed, can be designated as the critical concentration (CL25 - CL75), and the lethal concentration (CL75 - CL100) (Fig. 1). When making a diagnosis of fatal opiate poisoning, the forensic medical expert should pay attention to these parameters.

(Table 9).

Risk ranges of mortality and parameters of morphine concentration in blood plasma

Morphine concentration in blood (μg/ml) Determination of concentration	**Morphine concentration in blood (μg/ml) Determination of concentration**	**Morphine concentration in blood (μg/ml) Determination of concentration**
$CL_0 – CL_{25}$	0,44 и <	boundary
$CL_{25} – CL_{75}$	0,45 – 1,10	critical
$CL_{75} – CL_{100}$	1,11 и >	disastrous

Our data allow us to assert that to accurately establish the fact of fatal opiate poisoning, it is necessary to determine their metabolites in the victims' blood.

Results of postmortem detection of narcotic substances - opiates (morphine) in urine (or internal organs) can be used only as evidence of drug intoxication, confirming the use of opiates before death. Established parameters of the toxicity of drugs, for example, opiate (morphine), in the blood of victims made it possible to determine the concentration range, which is important for diagnosing drug poisoning with acute mortality.

The developed formalized probit plots of the "toxin concentration - effect" relationship allow for a quantitative assessment of the risk of death in all ranges of morphine concentrations in the blood, taking into account sex and age.

To determine the possible mechanisms of death in cases of opiate poisoning, determine the clinical picture of poisoning and the degree of decompensation of the main life support systems of the body, including the central nervous system, as well as the respiratory and cardiovascular systems. , learned. The obtained data were compared with the concentration of total morphine in blood plasma.

The results of the study showed that in the clinical stage of acute opiate poisoning, very specific damage is caused to the organs and systems: depression of the central nervous system and respiration, hemodynamic disturbances, myosis, cardiac arrhythmia. All these symptoms are, in general, toxic syndromes caused by poisoning. The severity of this syndrome and the individual symptoms of acute opiate poisoning in victims with varying concentrations of total morphine in blood plasma were different.

Among the signs of central nervous system damage, the greatest changes were associated with impaired consciousness. Depending on the type of stem, the leading role was played by the cessation of consciousness; stupor, stupor, coma were noted, and with severe respiratory disorders and deep cerebral hypoxia, convulsive syndrome appeared. Subsequently, in the somatogenic stage of acute intoxication, neurological symptoms were predetermined by cerebral edema and cerebrovascular accidents.

Victims brought in in serious and extremely serious condition experienced prolonged loss of consciousness and in 79.5% of cases did not regain

consciousness until death, the activity of the central nervous system was completely suppressed.

In mild and moderate severity, convulsions, vomiting, and superficial coma were noted.

In most cases, the victims of opiate poisoning suffered from respiratory disorders (91.6%), and in most cases, from mixed diseases. Its frequency in some cases sharply decreased (to the level of bradypnea) (45.3%; CI=0.40-0.55; p=0.05), in others - moderate (29.0%; CI=0.21-0.34; p=0.05). In fatal cases of acute poisoning, the most severe damage to the respiratory system was noted. Among the victims with a favorable outcome, a central type of respiratory disorder prevailed (26.8% of observations, and among the victims with an unfavorable outcome - 9.8%). Respiratory depression occurred even in victims who retained consciousness. Threatening decompensation of brain functions was manifested by an increase in respiratory rate and specific disorders of its rhythm.

In more than half of the cases (57.7%), respiratory distress was accompanied by the development of acute respiratory failure, which developed against the background of a coma. The frequency of superficial and deep coma at lethal concentrations of morphine in blood plasma was 4 times higher than in cases with critical concentrations and amounted to 43.0±10.1 hours and 28.1±2.4 hours, respectively; 11.7±0.7 hours and 5.0±1.8 hours.

In cases of acute opiate intoxication, the development of bronchitis and pneumonia prevails at the threshold and critical concentrations of morphine (58.4%; CI = 0.45-0.56; p = 0.05), and at lethal concentrations, the development of pulmonary edema was observed (19.9). %; CI=0.08-0.32; p=0.05). Exotoxic shock was observed in the majority of victims with a lethal concentration of morphine in the blood (53.4%).

Grouping the clinical and morphological signs of poisoning according to the value of their concentration limits is very objective, allowing for a more complete disclosure of the pathogenetic mechanisms of the body's dysfunction, as well as taking into account the individual reaction. The toxic substance in the blood can

change significantly; average values determined the concentration of morphine in the blood.

Thus, the dependence of the clinical picture of opiate intoxication on the initial level of morphine in the blood, which are systematized according to the detected concentrations or concentration limits, is presented in Table 10. To determine what specific signs of the pathological process can be detected in each zone of morphine concentration in blood plasma, the table should be used in daily practice.

Table 10.

Concentration thresholds for clinical presentation of acute opiate intoxication

PROPERTY NAME	**Frequency (%) (95% , p=0,05)**	**MORPHINE CONTENT IN BLOOD mcg/ml**		
		Border (0,1 – 0,44) n=107	critical (0,45 – 1,10) n=46	fatal (1,11 – 4,14) n=45
Mioz	88,9 (0,84-0,93)	***		
Bradipnea	74,2 (0,68-0,80)	***		
Traxeobronxit	30,3 (0,24-0,37)	***		
Prekoma	29,8 (0,24-0,37)	***		
Brain swelling	68,2 (0,61-0,75)		***	
Pulmonary edema	39,4 (0,33-0,47)		***	
Superficial coma	37,4 (0,31-0,45)		***	
Gipotenziya	32,8 (0,26-0,40)		***	

Pulmonary venous congestion	30,3 (0,24-0,37)		***	
Zotiljam	20,2 (0,15-0,26)		***	
Bradycardia	15,2 (0,10-0,21)		***	
Deep coma	21,7 (0,16-0,28)			***
Collapse of blood vessels	16,2 (0,11-0,22)			***
Exotoxic shock	14,6 (0,10-0,20)			***
Apnea	13,1 (0,09-0,19)			***
Mydriasis	6,6 (0,04-0,11)			***
Cardiac arrhythmia	2,5 (0,01-0,06)			***

Analysis of the data presented in this table shows that at the threshold concentration of the poison in blood plasma, clinical symptoms are minimal and manifest mainly with specific signs, but as the concentration becomes critical or fatal, the body's response to the syndrome becomes increasingly non-specific.

Since the reaction of the whole organism is systemic and the body as a system has very complex and interconnected functions, the method of factor analysis consists in constructing mathematical constructions in medicine, and interconnected (interrelated) signs are combined into factors according to the principle of generality of changes in the pathological process.

Using this method, you can not only establish cause-and-effect relationships, but also give them quantitative characteristics, i.e., measure the influence of factors on the overall pathological process. Thanks to this, the analysis will be objective and accurate, and the conclusions will be substantiated and reliable.

A factor analysis was conducted on 26 main indicators influencing the formation of the pathological process, the development of critical and terminal conditions. Factor loads less than 0.35 were not taken into account. The results of

the factor analysis revealed commonalities and differences in the body's reaction to opiate poisoning. The general point is that, first of all, the body responds to opiate poisoning with a set of symptoms characterizing its selective, specific reaction, but the response is not limited to this, but has a systemic character, reflecting the involvement of other systems of the body in the pathological process.

The most important signs of opiate poisoning are present in factor I. The elements of this factor reflect both the etiology of poisoning and the main specific effect (the presence of morphine in the blood, coma of varying depths) and its main clinical manifestation (respiratory depression, exotoxic shock), which indicates their main role in the outcome of poisoning. The structure of the factor under consideration confirms the integral, systemic nature of the body's response. The leading element in the body's integral response to opiate intoxication is the inhibition of the central system's activity (this is confirmed by the value of the factor load of deep coma - 0.92). On the contrary, other manifestations of opiate poisoning, generalized in factor IV (complications arising in the prehospital stage, cardiac arrhythmias, sex, age), are not informative signs, since they do not independently influence the outcome of poisoning.

Factor analysis of the clinical picture of opiate intoxication showed that central nervous system depression plays the most significant role in the pathogenesis of these intoxications. However, due to the close interdependence of all organs, each of them can change its function only by reflecting or causing changes in other organs and systems. This complicates the forensic medical examination of opiate poisoning, since in the clinical picture of poisoning, not only "specific" symptoms and symptom complexes are noted, but also many nonspecific effects. Such effects include disorders of the cardiovascular system, cardiac rhythm disturbances, pneumonia, infectious complications, and others that occur in the final (somatogenic) stage of intoxication.

Our multidimensional analysis of the clinical course of acute opiate poisoning revealed specific and nonspecific signs. However, to combine all these characteristics based on the principle of similarity, it is necessary to clearly construct and classify them. The clustering method should be used to synthesize all

elements of the clinical picture of acute opiate poisoning based on the principle of similarity.

Topological view of the relationship between individual clinical manifestations of acute opiate poisoning

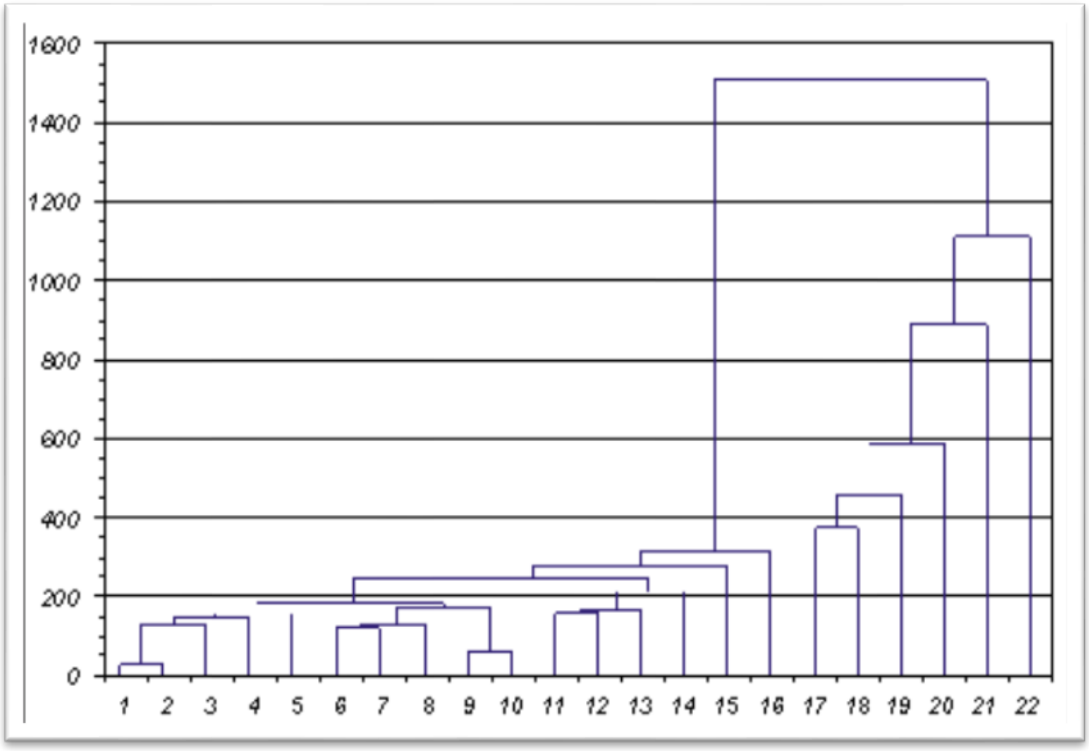


Figure. 15. Dendrogram of functional relationships in acute opiate poisoning.

Signs: 1 - result of poisoning; 2 - severity of the situation; 3 - precoma; 4 - superficial coma; 5 - deep coma; 6 - bradypnea; 7 - apnea; 8 - bradycardia; 9 - myosis; 10 - midriazis; 11 - hypotension; 12 - collapse of blood vessels; 13 - exotoxic shock; 14 - venous obstruction in the lungs; 15 - pulmonary edema; 16 - concentration of morphine in the blood; 17 - cerebral edema; 18 - pneumonia; 19 - encephalopathy; 20 - heart rhythm disorders; 21 - purulent intoxication; 22 - complications of the prehospital stage.

The process of combining properties into clusters always begins with the property listed first in their list. In this dendrogram, the characteristic of the classifier "result of poisoning" is in an extreme state, and the sequence of

subordinate features located next to it is automatically ordered according to the degree of proximity to the first.

This dendrogram shows that in acute opiate poisoning, two groups of local signs are distinguished - 1-16 and 17-22. The first group of characters (1-16), in turn, includes three more subgroups - 1-5, 6-10 and 11-14, as well as two separate characters - 15 and 16. There is a very large distance between them. The left (1-16) and right (17-22) clusters are approximately 1200 units, which indicates that the relationship between these two groups of properties is minimal. This dendrogram shows not only the complexity, but also a certain hierarchical order of functional-structural connections of the body during opiate intoxication. For example, in one zone there are indicators of the function of the central nervous system (suppression of consciousness at different depths). Initially, they act as independent elements, but later they are combined into graphs related to a specific function of the body, and at the level of 160 cluster distances, they are combined and reflect a certain commonality in the neurotoxic effects of opiates. Usually, in clinical practice, the pathological process of opiate intoxication, followed by death, has the following sequence: central nervous system depression, respiratory depression, cardiovascular insufficiency. However, these three syndromes, which are leading in the picture of intoxication on the dendrogram, are interconnected by several vertical and horizontal connections, reflecting their subordination, partnership, and interaction, as well as the concentration of morphine in the blood. , combined on a single graph. On the contrary, on the right wing of the dendrogram, there are signs that have the least impact on the outcome in the form of participation in the pathological process, in particular intoxication and fatal intoxication, but it is difficult to overestimate the significance of these signs, since they reflect the complications of the somatogenic phase.

An analysis of the relationship between the time of death and the clinical manifestations of victims of opiate poisoning was conducted, as a result of which four periods of acute opiate poisoning were identified: I - period of direct toxic effect (up to 12 hours), in which the specific effect of opiates is manifested, which is characterized by paralysis of the respiratory and vasomotor centers, and death is

caused by respiratory or cardiovascular insufficiency with a lethal concentration of morphine in the blood; II - period of early complications (12-72 hours), in which toxic substances are eliminated from the body and the first complications of poisoning are - hypotension and collapse, pulmonary edema, toxic coma, death from acute cardiovascular or respiratory failure, cerebral edema at the limiting or lethal concentration of morphine in the blood; III - period of late complications (72-288 hours), in which complications such as pneumonia and encephalopathy develop; at the time of death, there were no toxic substances in the victims' blood, but at the time of hospitalization, the concentration of morphine was moderate. threshold level and critical values; IV - the total period of complications or decompensation of somatic pathology caused by drug addiction (288-516 hours), which in the event of death as a result of a general infection or complications of chronic exogenous intoxication does not enter the victim's blood at the time of death, but the concentration of morphine at the time of hospitalization was at the limit.

Since not all symptoms reflecting the clinical picture of opiate intoxication have a significant influence on the occurrence of mortality, we conducted a correlation analysis and calculated the Spearman level correlation coefficient to establish a close relationship between the occurrence of mortality and various types of intoxications. Signs of the clinical course of poisoning. The results of the correlation analysis showed that the development of adverse outcomes in acute opiate intoxication is significantly influenced by factors reflecting severe respiratory dysfunction: apnea ($rs=0.8$; $p<0.05$), obstructive aspiration syndrome. ($rs=0.7$; $p<0.05$), pneumonia ($rs=0.6$; $p<0.05$); functions of the central nervous system: secondary coma ($rs=0.5$; $p<0.05$), prehospital coma ($rs=0.4$; $p<0.05$), encephalopathy ($rs=0.5$; $p<0.05$); dysfunction of the circulatory system ($rs=0.8$; $p<0.05$).

A retrospective analysis of medical records showed that in the first 72 hours of acute opiate poisoning, death occurred due to deep coma complicated by central respiratory failure, hemodynamic disturbances, and pulmonary edema. This is confirmed by a clear, statistically significant correlation between an unfavorable

outcome at a certain time interval and coma (rs=0.9; p<0.05), respiratory dysfunction (rs=0.8; p<0.05), pulmonary edema (rs=0.8; p<0.05). =0.6; p<0.05). In cases where death occurred later than 72 hours, the duration of the coma with such complications as pneumonia (rs=0.6; p<0.05) and encephalopathy (rs=0.9; p<0.05) was of primary importance (rs=0.5). p<0.05). And from the fifth day, in the somatogenic stage of acute opiate intoxication, pneumonia (rs=0.9; p<0.05) and encephalopathy in the form of secondary coma (rs=0.8; p) had the greatest significance for the development of mortality. <0.05). Thus, the noted clear and statistically significant relationship indicates that in the development of a critical and terminal state in the somatogenic period of poisoning, there is an almost isolated influence of one of these factors.

Along with the parameters of opiate toxicity and clinical and toxicological data, we also studied the morphological features characteristic of poisoning with acute mortality.

Among the internal organs and systems of the body, which play a key role in the implementation of somatic pathology caused by the use of opiates, the cardiovascular and central nervous systems can be distinguished first.

Morphological signs found in victims who died at the hospital stage were systematized, taking into account the toxicogenic and somatogenic phases of acute poisoning and the time of death of the victims.

During external, internal, and histological examination of the victims, the morphological picture of opiate poisoning was characterized by great diversity. However, when comparing the relationship of morphological manifestations with the chronology of poisoning, a certain sequence and interrelationship of clinical and functional manifestations and morphological equivalents characterizing them were noted.

The results of the analysis of the immediate causes of death in acute opiate poisoning are presented in Table 11.

Table 11.

Direct causes of death in acute opiate intoxication

NUMBER OF OPIATE POISONS NUMBER OF OPIATE POISONS	**NUMBER OF OPIATE POISONS NUMBER OF OPIATE POISONS**	
	abs.	**%**
I. Direct toxic effect (specific effect of opiates)		
Respiratory center paralysis (acute respiratory failure)	71	20,2
Paralysis of vasomotor centre (acute cardiovascular failure)	78	22,2
II. Early complications		
Collapse (acute cardiovascular failure)	58	16,5
Toxic pulmonary oedema (acute respiratory failure)	38	10,8
Toxic coma	11	3,1
III. Late complications		
Pneumonia	45	12,8
Encephalopathy	14	4,0
IV. Generalization of addiction complications, decompensation of somatic pathology		
Sepsis	7	2,0
exogenous intoxication with multiple organ	30	8,5

failure		
TOTAL	352	100,0

All cases with fatal outcomes and varying concentrations of morphine in blood and urine were divided into two groups. The first group consisted of victims who had more than 2.0 mcg/ml of morphine in their blood and more than 6.1 mcg/ml of morphine in their urine, and the second group consisted of all other victims who died.

Death from acute opiate poisoning occurred in all victims of the first group, while in the victims of the second group, fatal isodes arose as a result of decompensation of somatic pathology caused by prolonged drug use against the background of opiate poisoning.

Various morphological signs were identified, characterizing hemodynamic disorders, changes of a compensatory-adaptive, destructive, and inflammatory nature. Morphological equivalents of these nonspecific reactions are grouped by associating them with specific syndromes associated with general pathological, nonspecific complexes and not associated with any nosological form, which in some cases may be the direct cause of death.

Analysis of our results showed that the morphological picture in cases of death from the toxic effects of drugs caused by the specific effect of opiates did not differ in any specificity, and this was a characteristic feature of the changes in this group of deaths. The predominance of pathological phenomena caused primarily by hypoxia, hypotension, and systemic hemodynamic disorders.

Analysis of the clinical material showed that after 2-3 days, the signs of specific and nonspecific reactions of the body to the effects of opiates, corresponding to the toxicogenic and somatogenic phases, disappear, and the poisoning process proceeds to the next stage - the phase of late complications. In the group of deaths from late complications of opiate poisoning, the causes of death were pneumonia, encephalopathy, and a general infection.

Morphological changes in the victims of this group were characterized by severe and widespread inflammatory lesions of the lungs, post-hypoxic brain damage, and heart failure.

The distribution of the identified morphological signs in acute opiate poisoning depending on the toxicogenic and somatogenic phases is presented in Fig. 16.

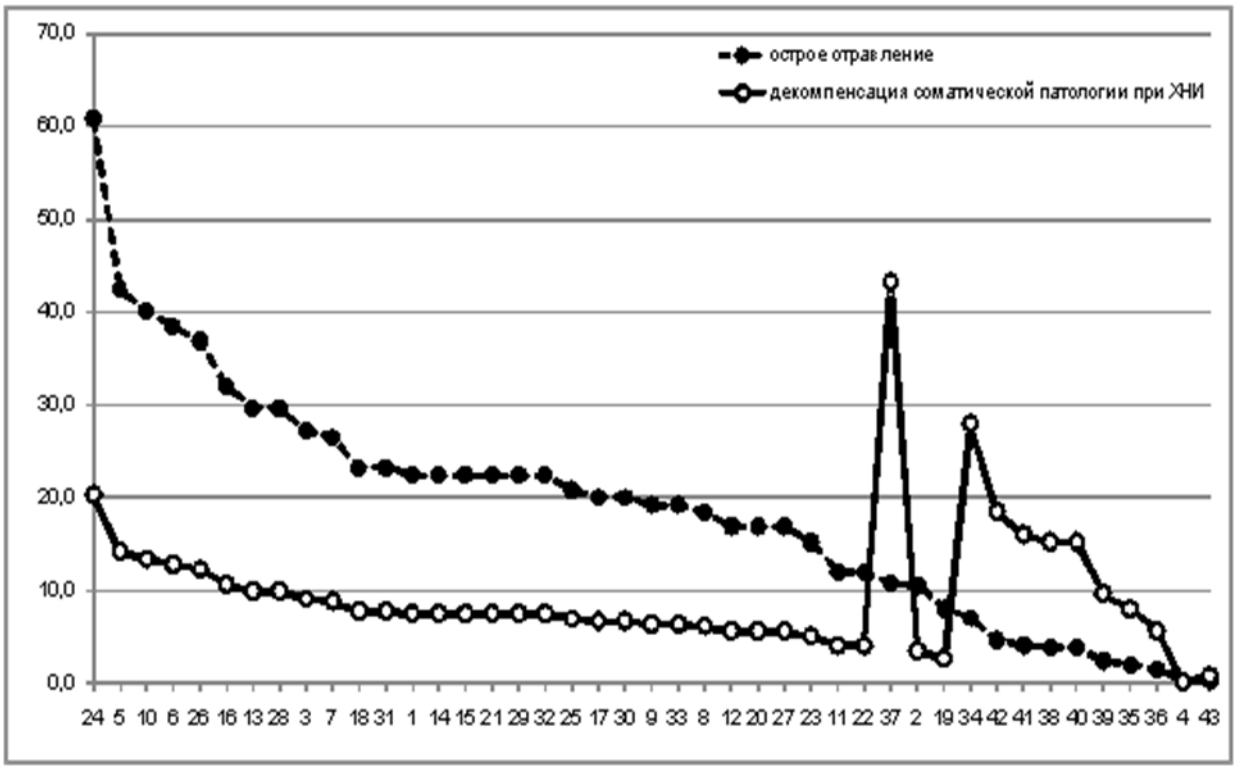


Fig. 16. Intensity and frequency of morphological signs depending on the toxicogenic and somatogenic phases of opiate intoxication (Kruskal-Wallis H-test, $p<0.01$). Acute poisoning, decompensation of somatic pathology, chronic intoxication

Signs: 1 - sharp saturation and cyanosis of the cadaveric spots; 2 - dilation and obstruction of the vessels of the eye membranes; 3 - cyanosis and cyanosis of the skin, mucous membranes, and nail beds; 4 - pallor of the skin and mucous membranes; 5 - venous occlusion of internal organs; 6 - increase, excess, and swelling of brain mass; 7 - excess and swelling of the pia mater; 8 - swelling of the

choroid plexuses of the brain; 9 - focal hemorrhages in the pia mater; 10 - increase in lung weight, obstruction, and swelling; 11 - dilation of the pleural lymphatic network; 12 - foamy fluid in the trachea, bronchi, nasal cavity, and oral cavity; 13 - focal bleeding under the pulmonary pleura; 14 - hemorrhage into the lung tissue; 15 - lung atelectasis; 16 - excessive stretching of the right atrium and vena cava with thick liquid blood; 17 - increase in heart mass; 18 - point and focal subendocardial hemorrhages; 19 - uneven blood supply to the myocardium; 20 - increase in liver mass; 21 - focal bleeding in the pancreatic tissue; 22 - bladder fullness; 23 - paretic dilation of the intestine; 24 - systemic circulatory disorders in the organs; 25 - predominantly perivascular cerebral edema; 26 - perivascular cerebral hemorrhages; 27 - pulmonary edema; 28 - intraalveolar bleeding; 29 - focal amphysema and atelectasis of the lung; 30 - interstitial myocardial edema; 31 - perivascular myocardial bleeding; 32 - focal bleeding in the pancreas; 33 - focal splenic hemorrhages; 34 - bilateral bronchopneumonia; 35 - abscessed bronchopneumonia; 36 - brain, heart, and kidney abscesses (sepsis); 37 - edema and ischemic damage to neurons; 38 - areas of delipoidization of the adrenal cortex; 39 - dystrophic changes in cardiomyocytes; 40 - changes in contracture and accumulated destruction of cardiomyocytes; 41 - dystrophic and anoxic changes in the brain; 42 - alveolitis; 43 - foci of pneumonia.

Thanatological analysis of the forensic medical examination material allowed us to identify the main types of terminal states in each specific case.

A comprehensive retrospective analysis of clinical data on the pre-mortem period of acute opiate poisoning showed that the development of a terminal state is associated with the occurrence of insufficiency of any vital organ (brain, heart, lungs). In some cases, the failure of such an organ is isolated, in others it is combined with the insufficiency of other vital organs.

Thus, the results of clinical and morphological analysis show that in each specific case, the development of the pre-death period is associated with pathological processes, which are not interpreted unambiguously due to the complexity of the developing cause-and-effect relationships. The underlying disease, acute opiate poisoning, leads to the development of various terminal

conditions, which, in turn, are characterized by various immediate causes of death. Thus, acute opiate poisoning, even during the victim's lifetime, can lead to the failure of any of the three vital organs - the heart, lungs, and brain - and the development of a corresponding type of terminal state, directly caused by the toxic effect of the drug.

Comparison of the main morphological manifestations of opiate poisoning with the immediate causes of death of victims and the chronology of the poisoning process allows us to identify the main stages of thanatogenesis. Analysis of the types of terminal states identified by us, determined by the mechanism of death, in comparison with the morphological picture of poisoning, shows that each of these types corresponds to a specific set of morphological features, according to which the groups of victims statistically significantly differ.

Depression of consciousness occupied the most important place in the group characterized by the predominance of the brain type of terminal state; to a lesser extent, respiratory and cardiovascular system disorders were noted, manifested in the form of bradypnea and bradycardia. , respiratory rhythm disorders and its sudden complete cessation. Analysis of thanatogenesis did not reveal any specific external and internal morphological features, except that the brain weight in most cases exceeds 1500 grams, and the brain substance is clouded in the section. Microscopic examination revealed the following results: blockage of the vessels of the brain substance with stasis in the brain, capillaries; perivascular hemorrhages were detected in various parts of the brain; pronounced perivascular and pericellular edema were observed; dystrophic changes were noted in the neurons of the cerebral hemispheres, their swelling and ischemic changes, such as wrinkles, hyperchromia of the nucleus, changes in the shape of the nucleus; ischemic and more serious changes in the neurons with tigrolysis in the subcortical and root regions and the appearance of shadow cells were detected. In the myocardium, venous congestion, moderate interstitial edema, dystrophic changes in cardiomyocytes, and periodic contractile changes in cardiomyocytes were observed. Pulmonary congestion, interstitial and intraalveolar edema, and bleeding were noted.

In the second group, characterized by the predominance of the cardiac type of terminal condition, the most clinically pronounced signs were reduced myocardial contractions, tachycardia and tachypnea, often shortness of breath, and bradycardia and bradypnea immediately before death. This likely indicated involvement in the pathological process of brain disorders and hypoxia. Changes in systemic hemodynamics were revealed, characterized by a collaptoid decrease in blood pressure. The most characteristic external visual signs were pallor of the skin and mucous membranes (state of the left ventricular terminal of the heart) or, conversely, cyanosis (state of the right ventricular terminal of the heart). Internal examination of the corpses revealed signs of pulmonary edema, as a rule, with acute venous congestion, dilated pleural lymphatic network, and a large stream of pinkish-pink fluid from the cut surface; similar fluid was also found in the bronchi, trachea, oral cavity, and nose. An increase in the weight of the lungs (1500-2000 g), liver, spleen, and kidneys was observed, which was associated with their swelling and excess. In most cases, the openings of the dilated right ventricle, right atrium, and vena cava are filled with thick liquid blood. Microscopic examination revealed the following results: uneven blood filling, interstitial edema, decreased severity of the transverse line of cardiomyocytes, contractile changes in the myocardium up to granular-accumulated destruction, and areas of Rego metachromasia. Cerebral, capillary and venous obstruction, perivascular and pericellular edema and isolated perivascular hemorrhages were noted, signs of ischemic cell damage were observed in cortical neurons; locations of venous obstruction, interstitial and intraalveolar edema and atelectasia were identified in the lungs; obstruction of central vessels and sinusoidal capillaries in the liver, dilation of Disse spaces, edema of periportal connective tissue; dystrophic changes were noted in the kidneys, tubular epithelium, and pronounced blockage of glomerular capillaries and medullary vessels.

In the third group, characterized by the predominance of the pulmonary type of terminal state, the most characteristic signs of the clinical course were disorders of ventilation-perfusion, diffusion, and filtration-absorption processes in the lungs, deterioration of airway patency, disorders in the biomechanics of respiration,

aeration, and pulmonary blood supply. Morphologically, they corresponded to the development of acute pulmonary failure syndrome. At the stage of external examination of the bodies of the victims, signs such as diffuse cyanosis of the skin, mucous membranes, and nail beds of the fingers were noted. Thus, in the comparative analysis of various terminal states encountered in our studies in cases of acute opiate poisoning, their differences were determined by the peculiarities of the course of the corresponding phases of acute poisoning, the subsequent development of complications associated with these poisonings. , in addition, the presence of concomitant pathology associated with chronic drug intoxication and reactivity associated with constitutional features.

Data from a retrospective analysis of the types of terminal conditions of patients who died from opiate poisoning show that the most common types of terminal conditions are the cardiac (42.4%), cerebral (20.8%), pulmonary (15.2%), and mixed (21.6%), and their development, as a rule, occurs due to new pathological processes caused by opiate intoxication.

Analysis of the structures of the immediate causes of death depending on the types of terminal states showed that if the cardiac and pulmonary types usually determine the occurrence of lethal consequences in the immediate causes of death, which are exotoxic shock and its consequences, then the cerebral type of terminal states most often develops with cerebral edema, encephalopathy, as well as exotoxic shock and its consequences. The development of a mixed type of terminal condition is determined by the immediate causes of death, such as pneumonia, cerebral edema, as well as exotoxic shock and its consequences.

Analysis of the results of clinical and morphological studies allows us to conclude that the manifestation of the general toxic effect of opiates manifests itself in systemic general damage to the vascular bed, which is associated with both hypoxia and systemic hypotension.

Systemic hypotension causes the phenomenon of the "boundary state of leukocytes," the release of lysosomal enzymes from parietal-fixed neutrophil granulocytes, which leads to diffuse damage to the endothelial lining, manifested by increased permeability of the vascular wall.

The periods of opiate intoxication identified during the study and the corresponding types of terminal states are characterized by a number of features. Morphological manifestations arising in cases of death of victims in the first period, when the body is under the direct toxic influence of opiates, and when the specific effect of opiates is clinically manifested, are characterized by a detailed description of hemodynamic disorders and are expressed by the syndrome of circulatory disorders, in addition, the following morphological signs were noted: microcirculation disorders, clay and stagnation of erythrocytes in the vessels of microcirculation, edema.

Morphological manifestations that appear in the second period, the period of early complications, characterized by the removal of the toxic substance from the body and the appearance of early complications of intoxication, arise from the process of exacerbation, contributing to the formation of hypoxia. Changes at the morphological level that determine the severity of poisoning include micro- and macrocirculation, bleeding, dysfunction of the respiratory and cardiovascular systems.

The manifestation of morphological changes in the third period is characterized by the period of late complications, dystrophic and anoxic changes in internal organs, dysfunction syndromes, insufficiency or deficiency of individual organs.

In stage IV, the period of generalization of complications or decompensation of drug-induced somatic pathology, morphological study shows a picture of changes in internal organs corresponding to chronic exogenous intoxication syndrome.

The results of the clinical analysis, compared with the morphological picture, showed that after taking opiates at toxic concentrations, acute respiratory failure develops, the development of which leads to paralysis of the respiratory center. This is a picture of a brain-type terminal condition in which paralysis of the respiratory center is the direct cause of death. In cases where respiratory failure does not develop immediately, mixed respiratory disorders occur, which include aspiration asphyxia and pulmonary edema. This, in turn, leads to respiratory failure, a terminal state of the lungs occurs, in which respiratory failure is the cause

of death. In such cases, hemodynamic disturbances develop against the background of hypoxia, manifesting in the brain in the form of posthypoxic encephalopathy, which is the main cause of death in the terminal state of the brain type, and in the heart: acute heart failure, which is the main cause of death in the terminal state of the heart type.

Analysis of our data shows that in most cases, death from opiate poisoning is clearly associated with the terminal state of the brain. In the presence of a combination of hemodynamic disorders and the direct toxic effects of opiates on the heart, a cardiac type of terminal state develops. In cases of death occurring in later periods, the causes of death are pneumonia, encephalopathy, or sepsis. A mixed type of terminal state develops, as failure syndromes occur in many organs.

Thus, the quantitative assessment of clinical and morphological signs of opiate intoxication using methods of multifaceted statistical analysis made it possible to identify a complex picture of intoxication not only by the interrelationship and generality of changes in the pathological process (factor analysis), but also by identifying signs (symptoms) with similar signs and compact groups of victims (cluster analysis).

Based on the obtained data, a series of normative graphs were created, with the help of which you can quickly assess the risk of adverse outcomes in patients, establish a characteristic clinical and morphological picture at any time of poisoning and severity. Determine the initial cause of death based on the initial level of morphine in the blood during the examination of corpses and chemical injuries in non-fatal poisonings.

Data from forensic chemical studies of biological fluids (blood and urine) allow for the determination of the exact cause of death in acute poisoning and an objective assessment of the severity of bodily injuries in acute drug poisoning, which objectively substantiates the conclusions of forensic medical examination with significant economic benefits.

Clinical and morphological analysis showed that the general toxic effect of opiates inhibits the central nervous system, vasomotor and respiratory centers, leading to general disorders of microcirculation and blood circulation, inhibition of

tissue metabolism, and decompensation of the functions of organs and the body as a whole.

Morphological changes in liver in chronic viral hepatitis in drug users and non-drug users

At this stage of our work, a complex of parameters for studying liver tissue, discussed in the previous chapter, was studied in chronic hepatitis in drug users and non-drug users.

The parameters of the ratio of the area of hepatocytes of the perinusoidal spaces and sinusoids to the total area of the parenchyma in the visual field in both groups did not differ significantly.

When determining the proportion of parenchyma area corresponding to hepatocyte nuclei cross-sections, it was found that in patients who did not use drugs, this value was, on average, 7%, and against a background of drug addiction - only 4% ($P<0.05$). In one field of view, with an increase of 400, in the absence of drug addiction, there were on average 4 binuclear and 5 large hyperchromic hepatocytes, and in the presence of drug addiction, this value was equal to 2 and 1, respectively. The average diameter of the hepatocyte nucleus was greater in the absence of drug addiction (7 μm, in drug addiction - 5 μm, the difference is statistically insignificant).

Consequently, chronic viral hepatitis against the background of drug addiction is characterized by a decrease in the intensity of hepatocyte regeneration, which is manifested by a decrease in the degree of their anisocytosis.

The proportion of parenchyma cross-sectional area attributable to fat vacuoles in the study group was 0.04, while in the comparison group (chronic hepatitis without drug addiction) it was only 0.02.

The average thickness of the central vein wall in drug addiction was 9.6±1.0 μm, and in its absence - 3.2±0.7 μm ($P<0.05$). The thickening of the wall occurred due to the proliferation of mature connective tissue and was accompanied by perisinusoidal sclerosis of the central lobes.

The average thickness of the arterial wall, which is part of the triad, was 10.9±0.5 μm in drug addicts and 5.9±0.8 μm in individuals with chronic hepatitis who did not use drugs ($P<0.05$), while the average diameter of the arteries was approximately the same in both groups and was 30 μm. Such thickening of the wall was observed in 80% of drug addicts and occurred both due to hypertrophy of smooth muscle cells and due to sclerosis of the intima and adventitia of blood vessels.

Thus, in drug addicts, the walls of the central veins and arteries of the portal tracts are significantly thickened. Apparently, these changes are not related to viral hepatitis, but are a reaction to disorders in the regulation of vascular tone, the causes of which can be both the aforementioned excesses of acute venous congestion and toxic damage to the autonomic nervous system, as well as emotional stresses, which are not uncommon for the lifestyle of drug addicts.

The ratio of stromal and parenchymal areas in the visual field was significantly greater in drug addiction and averaged 0.2, while in patients who did not use drugs, it was 0.07 ($P<0.05$).

Both in the study group and in the comparison group, practically all portal tracts were dilated. However, in drug addicts, the average cross-sectional area of the portal tract was larger and equal to 57665.3±5632.0 μm2, while in chronic hepatitis without drug addiction, this value was 43301.0±9860.0 μm2 ($P<0.05$). An even greater difference was revealed when measuring the average perimeter of the portal tract cross-section, which was 1275.8±59.7 μm against a background of drug addiction and 951.2±100.98 μm without it ($P<0.05$). It should be noted that the portal tracts, in which lymphoid follicles formed, had the largest cross-sectional area, and the perimeter of their cross-section also depended on the number and length of fibrous septa growing from the portal tracts into the parenchyma.

The portion of the portal tract cross-section perimeter, which falls on the foci of destruction of the border plate, was lower in drug addicts and averaged 0.1, and in individuals who did not use narcotic drugs - 0.2.

The proportions of the portal tract cross-sectional area corresponding to collagen fibers and blood vessels were approximately the same in both compared

groups, however, the proportion occupied by the bile ducts in drug addiction was greater than in its absence and constituted, respectively, 4.5 and 2.3% of the portal tract area ($P<0.05$). The number of bile ducts per single portal tract was also greater in drug addicts compared to non-drug patients (respectively 3.3 ± 0.4 and 1.1 ± 0.6, $P<0.05$), while their diameter was approximately the same.

Consequently, the proportion of portal tract cross-sectional area per ductula and the number of ductulas per single portal tract increases in drug addicts. This proves a higher degree of their proliferation, which is one of the markers of viral hepatitis C or the result of the cholestatic effect of narcotic drugs (Serov N.A. et al., 1999; Pott G., 1993).

The density of the portal tract inflammatory infiltrate in our study was determined by two methods: as the number of infiltrate cells per unit area of the portal tract cross-section (Pigolkin Yu.N., 2004; Ben Ari Z. et al., 1995) and as the ratio of the area occupied by infiltrate cells to the total area of the portal tract cross-section. In both determination methods, no significant differences were found between the compared groups for this parameter, however, its variance in drug addiction was higher, reflecting the fact that in hepatitis in drug addicts, portal tract infiltration occurred either with the formation of lymphoid follicles (with high cellular density) or less intensely than in hepatitis without drug addiction.

High values of stroma in the total volume of liver tissue, impaired maturation of collagen fibers, as well as an increase in the average perimeters and area of the portal tract against the background of drug addiction reflect a tendency towards fibroplastic and cirrhotic changes.

The relatively small portion of the portal tract cross-section perimeter corresponding to the foci of destruction of the boundary plate, as well as the tendency towards a lower density of inflammatory infiltration (including cases of lymphoid follicle formation) observed in drug addicts, confirm the conclusion about a lower inflammatory activity of hepatitis in this group.

Data on the cellular composition of the infiltrate are presented in Table 4.1.

Table 4.1.

Клеточный состав инфильтрата портальных трактов

Species of cellular elements	**Share in infiltrate, %**		
	against the background of drug addiction	**without drug addiction**	**P<0,05**
Фибробласты	7,4	10,8	-
Macrophages	8,9	2,7	+
Lymphocytes	76,6	86,2	-
Neutrophils	4,1	0,1	+
Eosinophils	2,5	0,09	+
Plasma cells	0,5	0,18	-

As can be seen from this table, statistically significant differences were revealed in the determination of macrophages, neutrophils, and eosinophils in the infiltrate, and the proportion of all three types of cells is higher in drug addiction, which confirms the fact of polymorphic inflammatory infiltrates in drug addicts. The focal accumulations of macrophages, sometimes containing hemosiderin, observed only against the background of drug addiction, in the portal tracts, including in the center of lymphoid follicles, are of particular interest.

The next stage of our research was the analysis of the qualitative and quantitative characteristics of liver changes depending on the age of drug addicts, using a comparison of different age groups according to Student's criterion and correlation analysis. As a result of these studies, we found no correlation between the degree of liver changes and the age of drug addicts. It was noted that liver damage during parenteral drug use not only occurs early but also progresses rapidly.

According to our studies, the course of chronic viral hepatitis against the background of narcotization is characterized by a number of features, including a high frequency of lymphoid follicle formation in the portal tracts and intralobularly, relatively low activity of portal hepatitis with significant severity of the lobular component of the inflammatory process, pronounced fibrosis and early formation of micronodular cirrhosis of the liver, pronounced proliferation of narrow bile ducts, increased content of neutrophils, eosinophils, siderophages, and ordinary macrophages in the infiltrate, as well as accumulation of the latter in the portal tracts in the form of granulomas.

The fact of the predominantly viral etiology of hepatitis developing in drug addicts, the prevalence of various viruses in this population, as well as their genetic and serological types, has been studied by many researchers (Loginov A.S. et al., 1999; Baozhaug T. et al., 1997). Our results also showed that liver damage is primarily caused by a viral infection, and drug intoxication is a factor causing the toxigenic pathomorphosis of this phenomenon. Furthermore, the research allowed for the identification of specific morphological manifestations of chronic viral hepatitis pathomorphosis in the context of drug addiction, i.e., changes in the course of hepatitis associated with drug intoxication, as well as signs of toxic liver damage.

As a result of the conducted research, a number of differences between drug-induced liver damage and similar liver damage without drug addiction were revealed. It should be noted that some of them can be explained by the fact that individuals prone to pathological attraction to psychotropic substances often combine them with alcohol.

The predominance of hepatocyte fatty degeneration in drug addicts, increased proliferation of the interlobular bile ducts, decreased regenerative activity of liver cells, and an admixture of eosinophils in infiltrates can be attributed to the toxic-allergic mechanism of liver damage by narcotic drugs and their admixtures (Serov V.V. et al., 1987). This explanation is also confirmed by the fact that when using drugs prepared at home and rich in toxic impurities, the content of eosinophilic leukocytes in the portal tracts of the liver is especially high.

In addition, the direct effect of drugs on the proliferative activity of hepatocytes, analogous to the suppression by opiates of neuroglia cell differentiation, is not excluded (Bogomolov D.V., 2000; Dolzhansky O.V. 2000).

The increased content of macrophages in infiltrates against the background of drug addiction, as well as their accumulation in the form of granulomas, can be explained by a reaction to intravenous administration, along with narcotic drugs, of a slightly soluble foreign material.

Currently, chronic hepatitis and cirrhosis of the liver are considered as stages of a single process, although in practice not every hepatitis leads to cirrhosis (Sutkin V.E. et al., 1998; Komarova D.V., Zinserling V.A., 1999). Criteria for its activity are considered to be the degree of necrotic changes and the proportion of portal tracts in a state of infiltration, based on which the IDA is determined (Knodell R.G. et al., 1981).

The morphological equivalent of the process stage is considered to be the degree of fibrosis, assessed by the GIS value (Ivashkin V.G., 1995; Desmet V.J. et al., 1994). Comparison of IHA and GIS allows for the classification of hepatitis into a particular section of the modern classification.

Chapter V. Morphological studies of the liver in chronic drug and alcohol intoxications, as well as in their combination

According to the data of forensic chemical studies and morphological features, it can be concluded that drug addiction is relatively often combined with alcohol abuse. In the literature, there is information that alcohol abuse increases the activity of chronic viral hepatitis C, in particular, due to the intensification of staged necrosis (Sekamova S.M. et al., 1998; Tanashchuk E.L. et al., 1998). Accordingly, the development of liver cirrhosis should also accelerate. Additionally, the acceleration of liver fibrosis and cirrhosis in drug addicts can be caused to some extent by increased frequency of mixed hepatitis (B+C) in this population. According to our observations and literature data (Pigolkin Yu.I., 2004), mixed hepatitis differs from monoetiological ones by the intensification of necrotic and inflammatory processes, which is manifested, first of all, by an increase in portal hepatitis activity.

At this stage of our research, we used the histomorphometric method for examining liver tissue in chronic alcohol intoxication (CHAI), chronic opiate intoxication, and their combination. The results of determining the main histomorphometric parameters of liver tissue according to group division are presented in Tables 5.1.-5.2.

CHAPTER V. MORPHOLOGICAL STUDIES OF THE LIVER IN CHRONIC DRUG AND ALCOHOL INTOXICATIONS, AS WELL AS IN THEIR COMBINATION

According to the data of forensic chemical studies and morphological features, it can be concluded that drug addiction is relatively often combined with alcohol abuse. In the literature, there is information that alcohol abuse increases the activity of chronic viral hepatitis C, in particular, due to the intensification of staged necrosis (Sekamova S.M. et al., 1998; Tanashchuk E.L. et al., 1998). Accordingly, the development of liver cirrhosis should also accelerate. Additionally, the acceleration of liver fibrosis and cirrhosis in drug addicts can be caused to some extent by increased frequency of mixed hepatitis (B+C) in this population. According to our observations and literature data (Pigolkin Yu.I., 2004), mixed hepatitis differs from monoetiological ones by the intensification of necrotic and inflammatory processes, which is manifested, first of all, by an increase in portal hepatitis activity.

At this stage of our research, we used the histomorphometric method for examining liver tissue in chronic alcohol intoxication (CHAI), chronic opiate intoxication, and their combination. The results of determining the main histomorphometric parameters of liver tissue according to group division are presented in Tables 5.1.-5.2.

Table 5.1.

Significance of the main parameters of liver histomorphometry in normal conditions, in opium addiction, and in chronic viral hepatitis without concomitant drug addiction

Indicator	**Norm**	**In drug addiction**	**Chronic viral hepatitis without drug addiction**
1	**2**	**3**	**4**
Cross-sectional area of stroma and parenchyma in the field of view	0,02	0,1	0,08
Proportion of parenchyma area corresponding to hepatocyte nuclei cross-sections in the field of view	0	0,04	0,02
The proportion of parenchyma area corresponding to interlobular infiltrate sections in the visual field	0	0,00099	0,0004
Perimeter of the portal tract cross-section, μm	662,7±90,4	1275,8±59,7	951,2±100,98
Portal tract cross-sectional area, μm2	20964,7±5467,2	57665,3±5632,0	43301,0±9860,0
The portion of the portal tract cross-section perimeter corresponding to the foci of	0	0,1	0,2

destruction of the boundary plate			
The proportion of portal tract cross-sectional area attributable to connective tissue fibers, %	29,6	38,4	35
The proportion of portal tract cross-sectional area attributable to inflammatory infiltrate cells, %	7,4	21,6	19

Continuation of Table 5.1.

Share of portal tract cross-sectional area per vessel, %	21,9	12,6	13
The proportion of the portal tract cross-sectional area attributable to the bile ducts, %	7,2	4,5	2,3
Number of bile ducts in the examined portal tract	1,5±0,6	3,3±0,4	1,1±0,6
Average thickness of the central vein wall	2,9±0,9	9,6±1,0	3,2±0,7
The average thickness of the artery wall that is part of the triad, μm	4,6±1,1	10,9±0,5	5,9±0,8

Median diameter of the artery comprising the triad	3,9	3,9	3,9

Table 5.2.

Significance of the main parameters of liver histomorphometry in isolated opium addiction, in its combination with chronic alcoholism, and in isolated chronic alcoholism

Indicator	**HNI**	**HNI and HAI**	**HAI**
1	**2**	**3**	**4**
The proportion of parenchyma area per section of fat vacuoles in the visual field	0,01	0,05	0,3
The proportion of parenchyma area corresponding to interlobular infiltrate sections in the visual field	0,0003	0,0009	0
Perimeter of the portal tract cross-section, μm	1237,5±76,9	1353,7±88,6	764,8±131,8
Portal tract cross-sectional area, μm2	58076,1±7450,9	51962,0±6761,4	31608,7±9156,0

Continuation of Table 5.2.

The portion of the portal tract cross-section perimeter	0,1	0,09	0

corresponding to the foci of destruction of the boundary plate			
The proportion of portal tract cross-sectional area attributable to connective tissue fibers, %	41	33	39,6
The proportion of portal tract cross-sectional area attributable to inflammatory infiltrate cells, %	20,3	22,1	9
Share of portal tract cross-sectional area per vessel, %	10,1	18,2	33,4
The proportion of the portal tract cross-sectional area attributable to the bile ducts, %	5,0	3,3	3,2
Number of bile ducts in the examined portal tract	3,68±0,54	2,63±0,6	1,2±0,7
Average thickness of the central vein wall	9,5±1,0	9,4±0,8	10,1±1,3

Microscopic examination in the comparison group (OAO against the background of IAI) revealed fatty degeneration of hepatocytes, sclerosis of the walls of central veins and portal tracts, which was combined with acute alcoholic hepatitis, manifested by infiltration of portal tracts with a significant mixture of neutrophilic leukocytes and the formation of alcoholic hyaline in hepatocytes.

Liver pathomorphology in drug poisoning and its significance in forensic medical practice

The escalating number of individuals struggling with drug addiction and the devastating outcomes associated with it have created significant theoretical and practical challenges for national healthcare systems [14, 88]. When addressing drug intoxication, it's important to acknowledge that the definitions of both narcotic substances and drug addiction are not universally agreed upon in current research. The designation of a substance as "narcotic" hinges on three interconnected aspects: its medical utility, its social impact, and its legal status. From a legal perspective, a substance is only classified as narcotic if all these criteria are met [51]. Consequently, drug addiction is understood as a collection of illnesses characterized by an intense desire for continuous consumption of escalating doses of narcotic or psychotropic substances. This condition arises from profound mental and physical reliance, leading to withdrawal symptoms when use is discontinued [90, 91].

Contemporary systems for categorizing narcotic drugs employ diverse approaches. For instance, classification by origin is frequently used, distinguishing between natural and semi-synthetic substances. Natural narcotics are further subdivided into those derived from plants, fungi, animals, and other sources [55]. Another prevalent method categorizes narcotics based on their chemical makeup, encompassing substances like opium alkaloids (phenanthrene series), amphetamines, cocaine (methylbenzoylectonine), cannabinoids, barbiturates, benzodiazepines, and phenothiazine drugs. While this chemical classification is useful for forensic scientists and pharmacists, it doesn't fully capture the physiological effects of these drugs, as chemically dissimilar substances can produce similar outcomes [51].

Currently, the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), offers subdivisions for statistical purposes, aiding in the tracking of drug and psychotropic poisonings. However, these classifications are primarily for administrative convenience and do not possess inherent scientific validity [42].

Various systems exist for categorizing narcotic substances, drawing upon established resources such as M.D. Mashkovsky's drug handbook and pharmacological texts by D.A. Kharkevich. Further insights come from clinical pharmacology works by D.R. Lawrence and P.N. Benitt, and clinical psychiatry literature from G.I. Kaplan and B.J. Sedok [29]. Krieger O.V. and colleagues propose a classification that includes opiates (both naturally derived and synthetic, along with their antagonists), substances that combine agonist and antagonist properties, drugs employed in medical treatments, central nervous system stimulants, and hallucinogenic agents.

Another approach categorizes drugs by their physiological effects, though this method is primarily relevant in a clinical context [51]. Combined classification systems, which integrate multiple criteria, are widely adopted. These are particularly prevalent in forensic medicine, where determining drug addiction after death necessitates the expertise of chemists to identify specific compounds in bodily tissues and morphologists to observe the physical manifestations of drug use [10]. For instance, N.V. Veselovskaya and A.E. Kovalenko [10] group narcotics into opiates, stimulants of diverse chemical origins, marijuana, hallucinogens (such as LSD, mescaline, psilocybin, psilocin), phencyclidine, amphetamine derivatives (methoxy and methylenedioxy), which, despite their chemical similarity to amphetamines, are distinguished by their unique effects. They also include synthetic opioid derivatives like methadone and tramadol, which act as opioids.

E.S. Shamsiev and his team [93] present a classification of major narcotic drug categories:

Sedatives: encompassing opiate drugs and barbiturate-based sleep aids.

Stimulants: including ephedrine and phenamine.

Psychedelics (consciousness-altering drugs): such as LSD, cannabis products, and other hallucinogens.

While these substances can all be misused as narcotics, their societal impact differs.

Due to the increasing mortality rates from drug use, there is a need to more thoroughly study the entire complex of pathognomonic signs accompanying opium addiction, including the correlation between clinical data and morphological manifestations in cases of suspected fatal drug poisoning [9, 29, 81]. Analysis of the results of sectional and histological examination of the organs and tissues of the bodies of drug addicts who died suddenly is quite often difficult due to the numerous comorbidities in the widespread nosological spectrum [9]. Diagnosis in these cases is based mainly on laboratory data. It is known that in 51-53% of cases of forensic chemical examination of biological fluids and tissues of drug addicts who died from poisoning, toxic substances are not detected due to rapid biotransformation of opium alkaloids [7].

Epidemiological findings indicate that ethanol, opium-derived narcotics, and, in certain regions, cocaine continue to be the primary illicit substances posing significant societal and health challenges, mirroring patterns observed in historical contexts [168]. Data from the Narcology Research Institute (Ministry of Health, Russian Federation) on 80 treated individuals (65 male, 15 female) revealed that heroin was used by 31.25%, while 43.75% consumed homemade opium preparations. Polydrug addiction, involving combinations such as heroin or opium with cocaine, or pervitin with ephedrone or hashish, affected 17.5% of this cohort [61]. A distinct category comprises individuals addicted to crudely prepared, illicitly manufactured narcotics, specifically "khanka," which are poorly purified derivatives of raw opium. The clandestine extraction of opium often co-produces other alkaloids alongside the psychoactive compounds. These additional substances substantially elevate the toxicity of such preparations upon ingestion. Beyond opium itself, these administered solutions may contain phenanthrene derivatives (e.g., morphine, codeine, thebaine), which are themselves potent drugs, as well as isoquinoline derivatives (e.g., papaverine, narcotine, narcein). While the latter are toxic in high doses, prolonged consumption even in smaller quantities can induce various pathological alterations in human physiology [73]. A more recent development is the emergence of "speedball," a combination of crack cocaine and

heroin. This mixture exhibits synergistic effects, resulting in a more severe and destructive impact on the body than either component used in isolation [10].

Novel psychoactive compounds, both naturally occurring and synthetically produced, are constantly emerging and pose a future risk for misuse [4, 92, 40]. Illustratively, prosidol [48], a novel narcotic analgesic, has recently been introduced into local medical settings. Research by S.N. Calderon et al. [113] details the creation of a potent and selective opioid receptor agonist, while O.A. al-Deeb [99] describes the characteristics of new phencyclidine derivatives.

Some researchers propose an inexhaustible array of narcotic substances existing in nature. Substantial evidence supports the presence of compounds like morphine, codeine, and acetylmorphine within various mammalian organs. The endogenous nature of these opiates is further substantiated by the identification of their precursor, thebaine, within the mammalian brain (13). More recently, non-peptide morphine-like substances, including tetrahydroisoquinolines and even morphine itself, have been confirmed in mammalian brain tissue and cerebrospinal fluid. The precise pathways for their biosynthesis remain an area of ongoing investigation. Evidence suggests that endogenous opiates can be generated from acetaldehyde, implying that alcohol consumption significantly elevates the levels of morphine-like compounds in the brain. The potential therapeutic applications of natural and synthetic opioid peptides, given their diverse regulatory functions, hold considerable promise for medical advancements [37].

The diagnostic challenge of identifying specific narcotic types has largely diminished in recent times. This is primarily because most lethal narcotics, such as ephedrone and hanka, have been supplanted by Afghan heroin. Despite this shift, distinct morphological characteristics associated with various drug addictions persist and hold value in expert analysis [52]. For instance, A.I. Ugryumov (1990) noted that while chronic opium intoxication doesn't present unique markers like alcoholic hyaline in alcoholism, its indicators develop rapidly and at an early age.

Presently, forensic medical assessment of drug poisoning relies on a combination of morphological findings and quantitative analysis of these substances in biological fluids and post-mortem tissues [15, 54, 96]. Forensic

chemical examination not only identifies the narcotic but also, by measuring its concentration in tissues, blood, and urine, can estimate the time since the last dose and the amount consumed [10, 15].

Historically, forensic medical diagnostics of drug poisoning initially focused on acute cases, with detailed morphological descriptions provided by forensic medicine pioneers like E. Hofmann (1912). This included descriptions of general asphyxial signs, typical case scenarios, and methods for detecting drug metabolites in tissues. Similar information is also available in contemporary guides [51]. Liver damage in drug addiction was first documented by W. Weimann in 1930, though its underlying mechanisms remained obscure for an extended period. Following the discovery of hepatitis viruses, it was established that liver pathology in drug users is predominantly virally induced, with the narcotics themselves playing a minor role [53].

Recent research has extensively documented numerous physical health issues among individuals with drug addiction [61, 73, 93, 135, 139, 157, 173, 204]. For instance, a study by M.L. Rokhlina et al. [61] involving 80 patients revealed a range of somatic indicators: skin flaccidity in 27.5%, dental caries and periodontitis in 80%, muscle atrophy in 38.8%, symptoms consistent with chronic bronchitis in 58.8%, dermatological and sexually transmitted infections in 63.8%, various cardiac arrhythmias in 53.5%, and evidence of hepatitis and hepatobiliary dysfunction in 60%.

The underlying mechanisms for these somatic manifestations likely involve both direct cellular harm and indirect damage resulting from dysregulation of neurohumoral systems or the introduction of infectious agents into the bloodstream [86]. Understanding the pathological processes and causes of death in drug addiction is complex due to the varied effects of psychoactive substances and contaminants, as well as widespread damage across multiple bodily systems, disrupting their interconnectedness at different organizational levels [86, 11].

Opioid drugs are recognized as having the highest toxicity among commonly available substances [10]. When specially prepared opioid drugs are used, the resulting organ damage is characterized by significant productive inflammatory

changes at the injection sites, vasculitis, and severe fibrosis, often leading to keloid formation. Skin examinations at injection sites revealed epidermal erosions, along with inversion and stratification abnormalities. In the dermis, prominent productive inflammatory infiltrates were observed, extending into the deep subcutaneous layers and even into muscle tissue. These infiltrates were primarily composed of histiocytes, with a sparse presence of plasma cells and lymphocytes [9, 73].

Certain psychoactive substances, specifically narcotics, have been observed to diminish the efficacy of the immune system. Morphine, for instance, has documented effects on immune regulation, mediated by its interaction with opioid receptors [12]. A broad range of immunosuppressive actions have been attributed to morphine and its related compounds [156]. These substances lead to a reduction in the quantity of lymphoid cells, hinder their growth and movement, decrease the proportion of T-helper cells, impede cytokine synthesis by T-lymphocytes, and diminish the cytotoxic capabilities of these cells [32, 105]. The underlying mechanisms for these disruptions include heightened lipid peroxidation, metabolic irregularities within lymphocytes, increased membrane fragility, and elevated enzyme release from lysosomes.

Consequently, individuals with opium dependence often exhibit a secondary immunodeficiency primarily affecting T-cells, alongside an activation of B-cells. This B-cell activation is evidenced by an amplified response to mitogens and elevated serum levels of immunoglobulin G and M compared to healthy individuals [24]. Paradoxically, despite B-cell activation, a reduced humoral immune response has been noted in opium addicts, particularly concerning antibody levels against hepatitis B and C viruses [102]. Furthermore, morphine has been shown to inhibit interferon production, suppress the phagocytic activity of polymorphonuclear leukocytes, and can even induce a decrease in neutrophil count [156]. Numerous studies also indicate that morphine impairs macrophage mobility [147]. In laboratory settings, experiments by D.L. Thomas et al. [196] demonstrated that heroin suppresses the proliferation of stimulated B-lymphocytes and inhibits the production of interleukin-2, a crucial signaling molecule in immune responses.

The immunosuppressive characteristics of many psychotropic drugs account for the frequent observation of changes in lymphoid organs, indicative of immune system exhaustion and dysregulation in individuals with severe neurological impairments. Histological examination of lymph node tissue in such cases often reveals either an overgrowth of follicles (in 45.5% of observations) or their atrophy, along with sinus histiocytosis. The thymus, upon histological analysis, shows signs of age-related changes in 85% of cases [34].

Currently, it has been shown that neurotransmitters can regulate immune system functions not only by influencing hormonal status but also directly. Immunodeficiency in drug addiction can also be related to the effects of hepatitis and HIV viruses [111].

The presented data allow us to explain some features of the course of infectious processes against the background of drug addiction. For example, R.R. Calderone and J.M. Larsen [113] note a high frequency of hematogenous vertebral osteomyelitis in drug addicts, with the causative agent most often being S. aureus.

Currently, it is believed that narcotic drugs affect mental and physiological functions due to their interaction with specific receptors, which are normally excited and inhibited by neurotransmitters and neuromodulators [41]. The effects of narcotic substances can be related to their effects on neurotransmitter synthesis, release, reverse capture, and metabolism [92]. Specific neurochemical and neurophysiological markers of specific psychotropic agents are known, but their detection is only possible in an experiment, at an extremely early stage after death, using complex and, as a rule, inaccessible neurohistochemical and immunohistochemical methods [40].

In drug addiction, the functions of the nervous and endocrine systems are carried out without proper physiological justification, i.e., the functional systems of the body act uncontrollably and chaotically. The morphological equivalent of these functional disorders has not yet been thoroughly studied [2].

Narcotic agents and impurities to narcotics (manganese, lead, organic solvents, etc.) have a pronounced, sometimes irreversible, pathological effect on the nervous system. According to the severity and speed of occurrence of neurological

disorders, drug addiction can be classified as follows: ephedrone, pervitin, barbiturate, opium, and hashish [39, 95].

A common pathology of drug addicts is acute disorders of cerebral circulation: cerebral and spinal infarctions, intracranial and subarachnoid hemorrhages. Histological studies revealed: brain swelling (93%), neuronal chromatolysis (75%), microcirculation disorders with perivascular hemorrhages (25%), vasculitis (21%), microthrombi (2%), small infarcts (2%), microglial lymphomonocytic nodes (9%) [52].

B.V.Sherstyuk et al. [95] described brain angiopathies in ephedrone addiction. Yu.V.Solodun et al. [73] vasculitis and catecholamine crises in CHI.

The clinical presentation and morphology of HIV encephalopathy, often combined with chronic drug addiction, have been described. It is characterized by opportunistic infections (toxoplasmosis, cytomegaly), progressive multifocal leukoencephalopathy, subacute microglious encephalitis characterized by the appearance of multinuclear macrophages [97]. HIV encephalopathy is considered a dystrophic-atrophic process in the CNS, accompanied by neuronal death, pronounced microglial reaction, vasculitis, accumulation of reactive astrocytes, focal leukodystrophy, and the appearance of multinucleated giant cells [46]. Numerous in-depth studies of HIV pathogenesis have shown that its target cells are cells containing CD4 receptors, including lymphoid growth cells, CNS neurons (approximately 2% of the population), and microglia cells [5].

The morphology of CNS lesions is quite rich, although the literature on this issue is presented only in fragmented reports (pigs). The author believes that it would be important and relevant to try to identify more specific morphological markers of the effects of narcotic drugs on the nervous system. According to P.Knapp, K.Hauser [134], this possibility may be related to the ability of narcotic drugs to affect the glial reaction that occurs in response to damage.

The widespread use of intranasal and inhalation routes of drug administration leads to a high frequency of direct toxic effects on the respiratory system. Acute complications of intoxication include pulmonary edema, intra-alveolar hemorrhages, and pneumopericardium. A common complication of

chronic "intravenous" drug addiction is pulmonary granulomatosis, which develops as a result of injecting dissolved medications intended for oral administration and occurs in 60% of drug deaths [94]. Morphologically, dystelectasis, acute unevenly expressed emphysema, stromal and interstitial edema, subsegmental acute hemorrhages, and focal hemosiderosis were also detected in the lungs. Focal pneumosclerosis is often observed.

In drug addiction, infectious lesions of the respiratory organs are common. Their development is often associated with the observed immunodeficiency in drug addicts, both associated with HIV infection and developing independently in response to drug administration. Pneumonia pathogens are cytomegaloviruses, pneumocysts, representatives of the conditionally pathogenic flora, mycobacteria, and often pathogenic fungi [70].

According to literature data, pneumomycoses, primary HIV pneumopathy, pneumocystis pneumonia, disseminated tuberculosis, Kaposhi's sarcoma, and malignant lymphomas are typical for drug addicts [73]. For HIV pneumopathy in drug addiction, according to Yu.V. Solodun et al. [73] are characterized by swelling, pulmonary tissue hyperemia, formation of hyaline membranes on alveolar walls, and their infiltration by lymphomonocytic cellular elements. A sharp thickening of the interalveolar septa is also typical, and hemorrhages and thrombosis in the vessels are not characteristic. A study of mortality among "intravenous" drug addicts in Moscow [72, 88] indicates that the cause of death in half of cases (50.9%) was a somatic illness. Acute heart failure was most frequently diagnosed (30.8%). Endocardial and cardiac valve damage in patients with drug addiction presents a very serious clinical problem, among which infectious endocarditis with tricuspid valve damage predominates [70].

According to Pigolkin Yu.I. [51], among the cardiovascular system lesions in chronic opiates, dilated cardiomyopathy prevailed (36.4%). In approximately 50% of cardiomyopathies, overdose of drugs was combined with moderate alcohol intoxication. Histologically, from the cardiovascular system, signs of ventricular fibrillation in the form of fragmentation of contracture-damaged cardiomyocytes, their twisting, paresis of microcirculatory vessels, vascular dystonia, and focal

acute hemorrhages were not uncommon (20.7% of observations). Dystrophic changes in cardiomyocytes occur in 59.2% of cases. The literature describes cases of dilated cardiomyopathy in drug addicts with characteristic clinical and morphological signs (cardiomegaly, non-coronarogenic fibrosing changes) [16]. According to O.V. Krieger et al. [29] Cardiomyopathy develops quite early and quite often (from 43% to 62% in different age groups) in drug addicts. The severity of narcogenic cardiomyopathy correlates with age. In drug-induced chronic intoxication, "intermediate" changes in the heart occur more frequently: fibroplastic processes, often cellular infiltration (sometimes in the form of intermediate myocarditis).

The high mortality rate of "intravenous" drug addicts is due to the frequency of infectious lesions of the cardiovascular system. Shabanov P.D. [90] noted the "weakness" of the myocardium with an increased probability of heart attack in all forms of drug addiction, as well as the diffuse and symmetrical nature of damage to the central and peripheral nervous systems as a result of the drug's toxic effect. Acute bacterial endocarditis combined with splenomegaly indicates the immunotoxic effect of opium alkaloids [12]. Bacterial endocarditis is accompanied by widespread vasculitis affecting almost all organs and systems, giving the disease the character of a universal vascular pathology [94, 95].

Drug addiction is accompanied by gastrointestinal tract damage [56]. When eating dried ground poppy, excessive use of dimedrol, the tongue becomes covered with a brown coating. Drinking "sultyga" solutions causes inflammation of the upper parts of the alimentary tract with ulcers and areas of necrosis. In 12.5% of drug addicts, signs of acute and subacute erosion of the gastric mucosa were noted. The use of cocaine and heroin can cause acute intestinal ischemia, peritonitis [94]. HIV infection, characteristic of drug addicts, leads to candidiasis, salmonellosis, shigellosis, and other gastrointestinal infections [73].

There is evidence in the scientific literature regarding the effects of opiates on the pancreas's incretory function, which, under the influence of drugs, significantly reduces insulin secretion [6].

In the pancreatic tissue of drug addicts, as a rule, autolysis and stromal edema are pronounced, which may be related to the peculiarities of thanatogenesis. Nevertheless, the signs of stromal fibrosis and lipomatosis are clearly defined (19% of cases), especially pronounced in the case of combined drug and alcohol poisoning. Apparently, alcohol plays the main role in their development [51]. O.V. Krieger et al. [29] note that pancreatic fibrosis and lipomatosis increase with age and, accordingly, with age of drug addiction. Often (24.1%) acute hemorrhages in the pancreatic tissue occur, apparently associated with asphyxiation.

Narcogenic kidney diseases have been studied in few works [56]. Macroscopic examination reveals kidney congestion - total or predominantly in the pyramids, which is associated with hypoxic thanatogenesis, common to all poisonings with so-called functional poisons. The parenchyma of the organs on the cut appears yellowish and flabby. Among such diseases, drug addicts often have various variants of immunocomplex glomerulonephritis associated with the direct administration of psychotropic agents ("heroin nephropathy") [155]. Yu.I.Pigolkin [51] described the signs of membranous glomerulopathy, which manifested as thickening of the basal membrane, capillary loops of the glomerulus and, apparently, is associated with an immune response to the circulation of foreign material in the blood.

For the reproductive system in SNIs, suppression of function with damage to the endocrine apparatus of these organs is characteristic [6]. In the testes, suppression of spermatogenesis with the proliferation of Leydig cells was often noted. In some places, lipofuscinosis has been detected. This can be related to both the direct gonadotoxic effect of narcotic drugs and intercurrent infections characterizing the so-called "lifestyle of drug addicts" [52]. It was noted that with maternal drug addiction, the body weight of the newborn is significantly lower than in the control group [153].

From the blood-forming organs, enlargement of the spleen (150 to 350g) and portal lymph nodes is observed [52, 150]. In 36.9% of cases, the spleen had a mass of more than 250 g, and in 76.6% - more than 200 g. The spleen had a tense capsule, was somewhat dense, with a juicy dark cherryy tissue on the cut, with an

underlined follicular pattern and a weak scrap [51]. At the same time, histologically, significant follicular hyperplasia with the formation of light centers was revealed in the lymph nodes. Hemosiderosis of the littoral macrophages of the spleen sinuses has been detected. In observations of bacterial endocarditis, the spleen had a septic appearance, histologically marked myelosis of the pulp and delimphatization of both T- and B-dependent zones. In the lymph nodes, follicular hyperplasia, often with smeared borders of lymphoid follicles. In the gallbladder of drug addicts, no special changes are found, except for fibrosis and swelling of the mucous membrane.

Many authors note that the most specific for drug poisoning should be recognized as pathological processes observed in the neuroendocrine system and liver [33, 47, 52, 55, 62, 87].

It has been established that under the influence of morphine and other opiates, increased secretion of growth hormone and prolactin occurs. Apparently, this phenomenon is related to the stimulating effect of opiates on the release factor of the growth hormone and their inhibition of somatostatin. Morphine and its derivatives can cause an antidiuretic effect by significantly releasing vasopressin into the blood. The influence of opiate drugs on the synthesis of thyroid-stimulating hormone by the pituitary gland was also noted. Even a single administration of opiates led to a significant decrease in the concentration of this hormone in the blood [6].

In the thyroid gland, a restructuring of histoarchitektonics has been observed with initial manifestations of macro- and microfollicular goiter formation; the stroma is often grossly fibrous with numerous sunken scars. Atrophy of the adrenal cortex against the background of its nodal restructuring is characteristic. To one degree or another, delipodination of the cortex is pronounced, correlating with the rate of death and corresponding to the phase of exhaustion of the generalized adaptive syndrome [66, 52].

The most vulnerable and early target for drugs is the liver. The main metabolism of xenobiotics occurs in the liver, therefore it is here that they accumulate in especially high concentrations and their toxic metabolites are

formed in this organ [87]. Furthermore, according to S.V. Shigeev [2002?], liver damage during parenteral drug use not only occurs early but also progresses rapidly. The highest mortality from acute heroin poisoning is observed when it is used for a year, and the duration of the period from the start of intravenous use of narcotic drugs to death also depends on the frequency of its administration: the longer it is, the faster the death outcome occurs.

Morphological changes in the liver, induced by the action of drugs, foreign substances, and the activity of the infectious-virus process, are diverse and often reflect simultaneously occurring adaptive degenerative and regenerative processes. In cases of drug addicts' death, hepatitis is detected in 79-100% of observations [6, 33].

According to Yu.I.Pigolkin [51], liver pathology allows us to indirectly judge which specific narcotic drugs were used. When comparing the data obtained on the Moscow and Volgograd material, statistically significant differences in the frequency of various liver lesions were revealed. In Volgograd, opium addiction was accompanied by the development of liver dystrophy only in 36.4% of cases, and chronic hepatitis - only in 28.4%. Apparently, this is due to the fact that Moscow's drug addicts use Afghan heroin, which is more toxic and often infected with hepatitis C virus already during production [73], while in Volgograd they use handmade narcotic drugs - "blackthorn," ephedrone, etc. [51]. This view aligns with literature data, according to which toxic-allergic granulomatous hepatitis and the presence of birefringent crystals in stellate endotheliocytes and portal tracts are typical for the use of specially prepared narcotics [73].

Macroscopically, the liver of drug addicts is usually enlarged (mass averaging 1937+116 g), with a smooth taut capsule and rounded (rarely acute) anterior edge. In almost half of the cases, organ mass exceeds 2000 g (hepatomegaly). The liver tissue can be of soft elastic consistency or slightly dense, on the cut, full-blooded, brownish-red, in 33% of cases with very small yellow foci that create the impression of a variegated pattern, in 14% of cases - with a diffuse yellowish tinge. Sometimes macroscopic data correspond to the so-called "large red liver" [69]. In 97% of cases, enlarged (up to 3x2.5x1.5 cm in size)

soft-elastic lymph nodes are found in the porta hepatis, not fused with each other or with surrounding tissues, and in cross-section are juicy, grayish-pink.

Information on the prevalence of various types of hepatocyte damage against the background of drug addiction is very limited and contradictory. For example, the frequency of fatty liver dystrophy, according to some sources, is 70%, of which 36.7% have diffuse fine-droplet dystrophy, 20.8% have focal varied-caliber dystrophy, and 12.5% have diffuse large-droplet dystrophy, while others account for 3.3% [51].

A more detailed description of the morphological changes in the liver of drug addicts is provided in the work of G.I. Nepomnyashchikh et al. [47]. According to these authors, the toxic effect of drugs manifests itself mainly at the intracellular level in the form of endoplasmic reticulum hyperplasia, a tendency towards an increase in the volume density of mitochondria and their size, and a more pronounced occurrence of intracellular regeneration foci than in the liver cells of patients who do not use drugs.

Histologically, foreign bodies in the form of crystals with a certain degree of granulomatous reaction of local macrophages are often found in the liver, as in the lungs. Thus, A.N.Elzouki and S.Lindgren [121] described a case of granulomatous hepatitis caused by prolonged use of a combined drug containing codeine and salicylates. L.A. Osick et al. [160], systemic amyloidosis, including liver damage, was observed in 16 patients who administered drugs (heroin, cocaine) intravenously and subcutaneously. All these patients had chronic purulent ulcers on their skin, which apparently contributed to the development of secondary amyloidosis.

The pathological process in the liver is one of the main somatic complications arising from the direct toxic effects of the used agents, as well as infection with hepatitis B, C, D, G viruses or their combinations due to intravenous drug administration [36]. Apparently, in some cases, it is the liver condition that determines the picture of withdrawal syndrome in drug addiction. Even during the period of narcological remission, patients with drug addiction often exhibit signs of liver damage [29].

The morphological manifestations of viral hepatitis under conditions of opiate intoxication may differ from the morphological picture of those without concomitant drug addiction, because immune mechanisms play a key role in the pathogenesis of this disease, and narcotic drugs, particularly opiates, can have a diverse effect on the immune system (51).

A number of authors argue that viral hepatitis, against the background of drug addiction, progresses more easily than in patients who do not use antiviral drugs. In particular, the prevalence of morphologically inactive and low-activity forms of hepatitis among drug addicts has been described [34, 53]. Rarity and low severity of periportal fibrosis have been noted in this category of patients [159]. According to some data, lymphoid follicles and bile duct damage are more characteristic of post-transfusion hepatitis, which is associated with greater activity of the inflammatory process in this route of infection [51]. Some researchers believe that viral hepatitis, on the contrary, is more severe in drug addicts [65].

CONCLUSION

1. Data from the epidemiological analysis of fatal drug and psychotropic substance poisonings clearly indicate that the problem of drug and psychotropic substance use remains relevant.

2. The results of the epidemiological analysis of lethal drug poisoning confirm the relevance and feasibility of the study.

3. Each case with a positive result of a blood and urine test for the presence of narcotic drugs and psychotropic substances should be considered as a fact confirming only the use of narcotic drugs before death, which does not unconditionally indicate the occurrence of death as a result of poisoning.

4. The absolute requirement for establishing the fact of acute poisoning with narcotic drugs and psychotropic substances leading to death is only their (or metabolites') quantitative detection in the blood.

5. Established indicators of toxicity of narcotic and psychotropic substances (opiates, morphine, amitriptyline, etc.) in the blood of victims made it possible to determine the concentration range, which is important for diagnosing poisoning with acute mortality.

6. Clinical and morphological analysis emphasizes that the general toxic effect of drugs (opiates) is manifested mainly by systemic damage to the vascular bed, associated with both hypoxia and systemic hypotension.

7. Chronic pathology of internal organs, caused by drug addiction, is a statistically significant background for the development of intoxication, which in most cases leads to acute death.

8. Comparison of the histological activity index (HAI) and the histological sclerosis index (HSI) allows not only to determine the main cause of death in drug poisoning, but also to determine the type of viral hepatitis.

9. The dynamics of morphological changes in the liver against the background of anesthesia in chronic viral hepatitis is characterized by a number of features, including relatively low activity of portal hepatitis with a high frequency of formation of lymphoid follicles in the portal tracts and intraocular lymphoid

follicles. Significant severity of the lobular component of the inflammatory process, pronounced fibrosis and early formation of micronodular cirrhosis of the liver, pronounced proliferation of the narrow bile ducts, an increase in neutrophils, eosinophils, siderophages, and simple macrophages, as well as infiltrates, the latter in the portal tract, such as granulomas.

10. The risk of death in individuals under 25 years of age from acute opiate poisoning is 3.8 times lower than in individuals over 25 years of age, in women - 1.3 times lower than in men, and in individual opiate poisoning - 6.8 times lower than during alcohol poisoning.

11. The formalized probit plots of the "toxin concentration - effect" relationship, developed by us, allow for a quantitative assessment of the risk of death in all ranges of morphine concentrations in the blood, taking into account sex, age, and duration of previous alcohol intoxication.

12. Death from opium poisoning can occur at any time of the four periods: I - period of direct toxic effect (up to half a day, 12 hours); II - period of early complications upon removal of the toxin from the body (up to 3 days, 12-72 hours); III - period of late complications (up to 12 days, 72-288 hours); IV - period of generalization of complications or decompensation of somatic pathology caused by drug addiction (up to 22 days, 288-516 hours).Drug addiction is one of the main medical and social problems of our time. Its spread leads to a continuous increase in mortality from acute poisoning, as well as from complications of chronic drug intoxications.

Currently, forensic medical diagnostics of drug poisoning is mainly based on the results of determining drugs in biological fluids and cadaveric tissues. Forensic chemical examination allows for the determination of the type of narcotic substance, and also, based on its concentration in blood tissues and urine, it is possible to judge the time elapsed since the last administration of the narcotic and the dose taken. Recently, methods for determining various narcotic substances in hair and nails have been developed, which allows for the diagnosis of not only acute but also chronic drug intoxication (Kryukov N.N. et al., 1999; Simonov E.A. et al., 2000). However, it should be taken into account that the range of narcotic

substances is increasing, and the methods of forensic chemical determination of narcotics in the body's biomedical environment are limited. In addition, the possibility of rapid elimination of narcotic substances from the body should be considered, as a result of which they cannot be determined by forensic chemical examination.

This situation is most characteristic of cases where the death from drug poisoning does not occur immediately and the victim was provided with medical assistance. In addition, in cases where narcotic substances are detected in low concentrations, it is very difficult to answer the question of whether this concentration is lethal.

Consequently, the need to develop additional criteria for forensic medical diagnostics of narcotic poisoning using morphological research methods is a pressing issue for forensic medicine.

We chose the liver as the object for morphological research in drug poisoning. As is known, the liver is the organ in which the main metabolism of xenobiotics occurs, therefore it is here that they accumulate in especially high concentrations and their toxic metabolites are formed in this organ. As a result, the liver becomes the main target for the manifestation of the toxicity of many drugs and other chemical substances (Chirkin A.A., 2000).

After the discovery of hepatitis viruses, many researchers began to adhere to the opinion that liver pathology in drug addicts in most cases has a viral etiology, and the role of narcotic drugs themselves is insignificant (Paties C. et al., 1987). In this regard, we considered it expedient to consider viral liver lesions in terms of the possibility of using their manifestations as additional diagnostic criteria for drug addiction. Hepatitis viruses are capable of causing four types of liver damage, which are often stages of a single infectious process: acute and chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. In this regard, we were interested in studying the morphological changes in the liver in chronic viral hepatitis in drug addicts and non-drug users. In addition to the toxic effects of narcotic drugs and their admixtures on the liver, ethanol can also play a role in liver damage in drug

addicts. According to modern concepts, alcohol consumption can cause three types of liver damage: fatty hepatosis, hepatitis, and cirrhosis.

There is information that changes in laboratory analyses characterizing liver damage in drug addicts infected with hepatitis C virus (HSV) are not related to virus replication, but to chronic alcohol intoxication, often accompanied by drug addiction (Seeff L.V. et al, 1975). In this regard, in this work, we presented the results of our liver studies in chronic drug and alcohol intoxications, as well as in their combination.

The most promising method for objectifying morphological research data is the transition from qualitative descriptions to quantitative analysis of histological preparations (Avtandilov G.G., 1984; 1990; 1998; Pigolkin Yu.I. et al., 1999). Another important advantage of quantitative research methods is that they allow for the presentation of data in a form convenient for computer processing, which allows for the creation of diagnostic models of the phenomena being studied (Tolstolutskiy Yu.D., 1995).

Applied to the problems of forensic toxicology, the morphological study of the liver has practically not been used until recently. Moreover, the qualitative changes in internal organs (including the liver) during drug addiction are nonspecific and cannot be used in expert practice as evidence (Pigolkin Yu.I. et al., 1991).

In this regard, the works of G.G. Avtandilov (1980, 1984, 1990) and Yu.I. Pigolkin (2004) served as the methodological basis for conducting liver histometric studies in this work.

We also used the recommendations of G.G. Avtandilov (1996) on measurement techniques using computer technology. This direction allows for a shift from subjective characteristics to objective ones, which increases the reliability of the integration of the obtained data, as well as ensures the convenience of their storage and the possibility of quick access to information, i.e., reduces the time spent conducting research.

The first stage of our research was the development of a system of morphometric parameters that comprehensively characterize the state of liver

tissue and their computer analysis techniques. For this purpose, liver tissue preparations taken from drug addicts were compared with those taken from individuals who did not use drugs and died from mechanical injuries. In each preparation, measurements were taken to characterize all the main liver microstructures in both normal and pathological conditions.

We used a set of parameters for a quantitative histomorphometric study of the liver according to the recommendation of Yu.I. Pigolkin (2004). Furthermore, to assess the activity of viral hepatitis and the severity of fibrosis in it, semi-quantitative determination of these parameters was carried out in 8 observations using the method of R.I. Knoell et al. (1981).

For 30 visual fields, the severity of necrosis was assessed (missing - 0 points, insignificant - 1 point, moderate - i.e., less than half of the portal tracts - 3 points, more than half - 4 points, bridge-like - 5 points, by prevalence multilobular - 10 points).

The degree of fibrosis was assessed by the sclerosis histological index (GIS), which was determined according to the following scheme: absence of fibrosis - 0 points, expansion of portal tracts due to fibrosis - 1 point, porto-portal septa - 3 points, cirrhosis - 4 points.

Comparison of IHA and GIS allowed us to classify hepatitis as a specific division of the hepatitis classification (Serov V.V., 1999) and to consider the correspondence of activity to the severity of fibrocyrotic changes.

In the next stage of our research, we studied the morphological changes in the liver in chronic viral hepatitis in drug addicts and non-drug users.

Here, the complex of parameters for studying liver tissue, specified in the previous chapter, was also used.

As a result of the conducted research, it was established that chronic viral hepatitis against the background of drug addiction is characterized by a decrease in the intensity of hepatocyte regeneration, which manifests as a decrease in the degree of anisocytosis.

In drug addicts, the walls of the central veins and arteries of the portal tracts are significantly thickened. In our opinion, these changes are not directly related to

viral hepatitis, but are a reaction to disorders in the regulation of vascular tone, the cause of which can be both excesses of acute venous congestion and toxic damage to the autonomic nervous system, as well as emotional stresses, which are not uncommon for the lifestyle of drug addicts.

The ratio of stromal and parenchymal areas in the visual field was greater in drug addiction and averaged 0.2, while in patients who did not use drugs, it was 0.07 ($P<0.05$).

Both in the study group and in the comparison group, practically all portal tracts were dilated. However, in drug addicts, the average portal tract cross-sectional area was significantly larger.

The number of bile ducts per portal tract was also higher in drug users compared to non-drug users.

Thus, the proportion of portal tract cross-sectional area per ductula and the number of ductulas per single portal tract increases in drug addicts. This proves a higher degree of their proliferation, which is one of the markers of viral hepatitis C or the result of the cholestatic effect of narcotic drugs (Serov I.A. et al., 1999; Pott G., 1993).

The density of the portal tract inflammatory infiltrate in our study was determined by two methods: as the number of infiltrate cells per unit area of the portal tract cross-section (Pigolkin Yu.I., 2004) and as the ratio of the area occupied by infiltrate cells to the total area of the portal tract cross-section. In both determination methods, no significant differences were found between the compared groups for this parameter, however, its variance in drug addiction was higher, reflecting the fact that in hepatitis in drug addicts, portal tract infiltration occurred either with the formation of lymphoid follicles, or less intensely than in hepatitis without drug addiction.

High values of stroma in the total volume of liver tissue, impaired maturation of collagen fibers, and an increase in the average perimeter and area of the portal tract against the background of drug addiction reflect a tendency towards fibroblastic and cirrhotic changes.

When studying the cellular composition of portal tract infiltrates, statistically significant differences were revealed in the determination of macrophages, neutrophils, and eosinophils in the infiltrate, and the proportion of all three types of cells was higher in drug addiction, which confirms the fact of polymorphism of inflammatory infiltrates in drug addicts.

When analyzing the qualitative and quantitative characteristics of liver changes depending on age groups, we found no correlation between the degree of liver changes and the age of drug addicts. It should be noted that liver damage during parenteral drug use not only occurs early but also progresses rapidly.

According to our research, the course of chronic viral hepatitis against the background of narcotization is characterized by a number of features, including a high frequency of lymphoid follicle formation in the portal tracts and intralobularly, relatively low activity of portal hepatitis with significant severity of the lobular component of the inflammatory process, pronounced fibrosis and early formation of micronodular cirrhosis of the liver, pronounced proliferation of narrow bile ducts, increased content of neutrophils, eosinophils, siderophages, and ordinary macrophages in the infiltrate, as well as the accumulation of the latter in the portal tracts in the form of granulomas.

Our studies also confirmed the fact that hepatitis developing in drug addicts is predominantly of viral etiology.

Drug intoxication is a factor causing the toxigenic pathomorphosis of this phenomenon.

As a result of our research, a number of differences between drug-induced liver damage and similar liver damage without drug addiction were revealed. Some of them can be explained by the fact that people who have a pathological attraction to drugs often combine them with alcohol.

In this regard, the next stage of our research was the study of the above-mentioned parameters of the morphometric study of the liver in chronic drug and alcohol intoxications, as well as in their combination.

According to our research results, alcohol consumption by drug addicts leads to increased damage to hepatocytes, which manifests as increased fatty

degeneration, increased lobular hepatitis activity, the appearance of neutrophil inclusions in the inflammatory infiltrate, and increased sclerotic processes, leading to an increase in the perimeter of the portal tract cross-section due to connective tissue growth. Quantitative analysis of these processes can be recommended for use by forensic medical experts when it is necessary to conduct a differential diagnosis of chronic alcohol intoxication against the background of drug intoxication.

Thus, we revealed peculiarities in the course of pathological processes in the liver during combined intoxication with narcotic drugs and alcohol, in particular, an increased frequency and severity of morphological markers of alcoholism in individuals who consume both alcohol and narcotic drugs, compared to individuals who consume only narcotic drugs. According to our data, alcohol consumption by drug addicts leads to increased fatty degeneration, increased lobular hepatitis activity, the appearance of neutrophil inclusions in the inflammatory infiltrate, and increased sclerotic processes, leading to an increase in the perimeter of the portal tract cross-section due to connective tissue growth.

Our studies have shown that markers of chronic alcohol intoxication are significantly more common in those who died from combined acute alcohol and opiate poisoning than in those who died from isolated acute opiate poisoning, which can be explained by the role of ethanol in the development of these morphological changes. In particular, the proven morphometrically greater severity of fatty degeneration in combined poisoning is one of the results of drug addicts' tendency to consume narcotic drugs in combination with alcohol (Ruttenber A.J. et al., 1990), since chronic hepatitis C without combined IAI is most characterized by small-drop fatty degeneration of hepatocytes (Nepomnyashchikh G.I. et al., 1999).

Alcoholic liver damage, in our opinion, explains to some extent not only the greater severity of fatty degeneration but also the accelerated development of liver cirrhosis, as well as the presence of neutrophilic leukocytes in infiltrates in drug addicts.

Consequently, combined intoxication with opiates and alcohol is characterized by an increase in hepatocyte damage, which manifests as a combination of signs of viral-toxic and alcoholic liver damage. Morphologically determined signs of its alcoholic damage allow for a differential diagnosis between isolated and combined opium intoxication.

To solve these tasks, we used the method of Yu.I.Pigolkin (1999, 2004) - a method of histomorphological liver examination to identify signs of narcogenic pathomorphosis of chronic viral hepatitis, toxic and alcoholic liver damage, which are additional diagnostic criteria for isolated chronic opium intoxication and its combination with alcohol.

PRACTICAL GUIDELINES

A thorough, tailored strategy for diagnosing fatal intoxications from illicit and mind-altering substances in forensic medicine enables a comprehensive, structured examination of these violent fatalities. This approach forms the foundation for its broad application, aiming to elevate the caliber and impact of such investigations and analyses.

When performing a forensic medical assessment of deaths caused by narcotic and psychotropic substance poisoning, the determination should rest upon a combined evaluation of clinical, anatomical, and chemical findings. This must incorporate a quantitative appraisal of mortality risk at specific morphine levels, considering all pertinent factors. Only through this methodology can a conclusion of fatal poisoning be affirmed. Consequently, in other scenarios, the presence of poisoning or drug intoxication that did not result in death should be acknowledged. For a definitive confirmation of fatal poisoning, it is imperative to quantitatively identify the metabolites of these substances exclusively within blood samples.

Mortality due to opiate intoxication can manifest across the full spectrum of detectable concentrations. Nevertheless, when diagnosing a fatal opiate poisoning, primary focus ought to be directed towards the concentration ranges of the drugs and psychotropic substances themselves.

Distinctive structural alterations indicative of drug-induced changes in chronic viral hepatitis can serve as markers to distinguish hepatitis that develops in individuals with substance use disorders.

LIST OF USED SOURCES

1. Avtandilov G.G. Introduction to Quantitative Pathological Morphology.-M,1980.-P.213.

2. Alekseev Yu.D. Age-related morphology of male sex glands // Forensic Medical Expert.-1998 -No6.-P.41-43.

3. Aspects of forensic medical diagnostics of acute opiate poisoning /E.Yu.Pavlenko, L.N.Zimina, I.E.Galankina, M.V.Barinova //Forensic Medical Examination. - 2003. - No. - P. 10-14.

4. Astashkina O.G., Papyshev I.P., Stolyarova E.P. Determination of myoglobin concentration in biological fluids and tissues by passive hemagglutination method in the postmortem period // Medical Expertise and Law. - 2011. - No. - P.47-49.

5. Berezovskaya M.A., Korobitsina T.V., Sherstyanov A.S. Indirect methods for assessing the prevalence of non-medical drug use // Bulletin of the Siberian Law Institute of the FSKN of Russia. 2014. No. 4. P. 106-110.

6. Bogomolov D.V., Pigolkin Yu.I., Dolzhansky O.V. Morphometric study of neuroglial complexes of the brain in forensic medical diagnostics of drug addiction. //Forensic Medical Examination. - 2004. - No 4. - P. 18-19.

7. Bonitenko E. Yu. et al. Modeling of Toxic Comes Caused by Depriming Substances // Proceedings of the Institute of Toxicology, Dedicated to the 75th Anniversary of its Founding / edited by S. P. Nechiporenko. SPb., 2010. P. 16-30.

8. Borodin S.A. Pathomorphology and forensic medical assessment of myocardial changes in acute and chronic combined intoxication with opiates and ethanol: abstract of diss.... cand. med. sciences. Novosibirsk, 2006. - 21. p.

9. Vaisov S. B. Drug and Alcohol Addiction: A Practical Guide. - St. Petersburg: Science and Technology, 2008. - 268 p.

10. Vaisov A.Sh., Shamsiev E.S., Iskanderov A.I. Diagnostic criteria of dermatological changes in heroin addiction in forensic medical practice. //Dermatovenereology News. - 2006. - No. 3.- P. 25-27.

11. Veselovskaya N.V., Kovalenko A.E. Narcotics. - M.: Triad-X, 2000. - 2004.

12. Golovko A. I. Narcology. General Issues and Pathogenesis of Chemical Dependencies SPb.: Artikom, 2008. 487 p.

13. Jalilov F.S., Akhmedjanov I.G., Madgazina M.A. Study of the qualitative analysis of amitriptyline in forensic chemical practice by the method of thermodesorption surface ionization spectroscopy. Republican Center for Forensic Examination named after Kh.Sulaymonova Materials of the Republican Interdepartmental Scientific and Practical Conference "Expert of the Republic of Uzbekistan: Results and Directions of Development." Tashkent, 2007. - P. 75-77.

14. Jalilov F.S., Tojiev M.A., Saidkarimova N., Ergashova I., Ochilov M. Qualitative analysis of the drug Rexetin by the method of thermodesorption surface ionization spectroscopy. "Current Issues of Education, Science and Production in Pharmacy," materials of the scientific-practical conference. Tashkent, 2008. - P. 338-339.

15. Jalilov F.S., Ochilov M., Alimova F., Tojiev M.A. Qualitative analysis of the drug Fevarin by the method of thermodesorption surface ionization spectroscopy. Materials of the XVI scientific-practical conference of students and young scientists on the topic "Topical Problems of Medicine." Urgench, 2009.

16. Jalilov F.S., Tadjiyev M.A., Akhmedjanov I.G. Development of a methodology for the thermodesorption surface-ionization spectroscopic analysis of some antidepressants.// Materials of the VII National Congress of Pharmacists of Ukraine, Kharkov, 2010. September 14-17. -P. -151.

17. Jalilov F.S., Tojiyev M.A. Application of the thermodesorption surface-ionization spectroscopy method in the analysis of paroxetine. "Pharmacy: Current State, Achievements, and Prospects" collection of materials from the international scientific-practical conference. Almaty, 2010. - P. 20-24.

18. Jalilov F.S. Analysis of carbamazepine by the method of thermodesorption surface ionization spectroscopy. // Pharmaceutical Journal. - Tashkent, 2012. -No1. -P. 46-49.

19. Zhamlikhanov N.Kh., Fedorov A.G. Structure, features of the clinical course and complications of acute poisoning with psychoactive substances among children and adolescents // Healthcare of Chuvashia. 2009. No. P. 26-30.

20. Zarafyants G.N., Basharin V.A. Aspects of forensic medical diagnostics of combined poisoning with neurotropic poisons //Scientific notes of St. Petersburg State Medical University named after Acad. I.P. Pavlov. 2012. Vol. XIX. No. P. 54-57.

21.Ivanets N. N. Mortality of Drug Addiction Patients in the Russian Federation. Analysis of Federal Statistical Observation Data // Questions of Narcology. 2008. No. P. 105-118.

22. Ivanza N.N., Anokhin I.P., Vinnikova M.A. Narcology: National Guide. - M.: GEOTAR_Media, 2008. - 720 p.

23. Studying the criteria for early diagnosis of HIV infection in drug users /A.S.Akbarov, M.M.Khakimov, A.Sh.Vaisov et al. //Materials of the international scientific and practical conference "Achievements and problems in the study of infectious diseases." - Andijan, 2003. - P.125-126.

24. Kandiba T.S., Dvalidze S.V., Shaxvorostov A.V. Aspects of forensic medical diagnostics of heroin poisoning. //Current issues of the theory and practice of forensic medical examination. Krasnoyarsk, 2007. - Issue. 5.

25. Kaurov Ya.V., Larchenko A.V., Artemenko A.G., Gnelitskiy G.I., Mudrova S.A., Pankov A.V. Smoking Mixtures: Medical and Social Aspects //Journal of Scientific Articles Health and Education in the 21st Century. 2014. Vol. 16. No 4. P. 162-164.

26. Kuligin A. V. Reanimation and intensive therapy of patients in the acute period of coma: abstract of diss.... Saratov, 2008. 33 p.

27. Litvitsky P.F. Drug Addiction, Toxic Addiction, Poisoning // Issues of Modern Pediatrics. 2014. Vol. 13. No 3. P. 51-60.

28. Lyashev Yu.D., Knyazev A.I., Solin A.V. Influence of opioid peptides on free radical oxidation processes in bone regenerate after fracture //Pathological Physiology and Experimental Therapy. - 2005. - No. - P. 19-20.

29. Morphological diagnosis of narcotic intoxications in forensic medicine /Edited by a member-cor. Yu.I.Pigolkina. - M.: Medicine, 2004.

30. Nevolin A.N., Grinberg L.M., Kondrashov D.L. Pathomorphology of Talc-associated changes in internal organs in intravenous drug addiction // Ural Medical Journal. 2011. No. 1 (79). P. 39-43.

31. Novoselov V.P., Savchenko S.V., Bgatova N.P., Kuznetsov E.V., Titarenko B.F., Starostin S.A. Assessment of the state of the myocardium and the ultrastructure of its microvessels in chronic intoxication with opiates and ethanol // Pathology of Circulation and Cardiac Surgery. 2011. No. P. 67-70.

32. Novoselov V.P., Savchenko S.V., Kuznetsov E.V., Titarenko B.F. Assessment of ultrastrural changes in cardiomyocytes during chronic intoxication with opiates and ethanol // Siberian Medical Review. 2011. No. 5 (71). P. 17-20.

33. Novoselov V.P., Savchenko S.V., Borodin S.A. Morphology of the myocardium in acute and chronic intoxication with opiates and ethanol // Siberian Medical Review. - 2010. - No 4. - P.39-43.

34. Pavlenko E.Yu. et al. Aspects of forensic medical diagnostics of acute opiate poisoning // Forensic Medical Examination - 2003. - 3. - pp. 10-14.

35. Papyshev I.P. Myoglobin of blood, urine, myocardium and skeletal muscle - what a possible additional criterion for lethal poisoning with alcohol and opiate drugs // Bulletin of the Russian State Medical University. - 2010. - No. - P. 69-72.

36.Papyshev I.P., Chernyaev A.L., Samsonova M.V., Kildyushov E.M., Obernikhin S.S., Mikhaleva L.M. Forensic medical assessment of the content of myoglobin in blood and urine in certain types of lethal poisoning // "Selected issues of forensic medical examination." Khabarovsk, 2009. - No. 10, pp. 93-95.

37. The liver of drug addicts /A.S.Loginov, L.Yu.Ilchenko, T.M.Saregorodtseva, et al. //Therapeutic Archive. - 1999. - No. - P. 39-44.

38. Pigolkin Yu.I., Gasanov A.B. Comparative morphological characteristics of immune deficiency in opiate drug addiction and chronic alcohol intoxication //Forensic Medical Examination. - 2010. - No1. - P. 26-29.

39. Pigolkin Yu.I., Dolzhansky O.V., Golubeva A.V. Forensic Medical Diagnostics of Chronic Drug Intoxication Based on Morphological Data //Forensic Medical Examination. - 2012. - No1. - P. 34-37.

40. Pigolkin Yu.I., Dolzhansky O.V. Comparative characteristics of morphological changes in the brain in acute blood loss against the background of drug intoxication and in individuals who have not used drugs / // Forensic Medical Examination. - 2010. - No2. - P. 4-6.

41. Pigolkin Yu.I. Morphological Diagnosis of Drug Intoxication in Forensic Medicine. - M.: Medicine, 2004. - P. 304.

42. Porodenko V.A., Travenko E.N. State of blood and liver monoamine oxidase in fatal alcohol intoxications // Forensic Medical Examination. -1999. - Vol.42, No. 4. - P. 22-24.

43. Pravdyuk M.F., Morozov Yu.A., Apajikhova R.A., Karginova O.E., Tanklaev K.M. Problems of inappropriate use of catadolone and the possibility of its chemical-toxicological analysis in urine // In the collection: Pharmacological science - from theory to practice All-Russian Scientific Internet Conference with international participation. PaxGrid Virtual Conference Service; IP Sinyaev Dmitry Nikolaevich. Kazan, 2014. P. 74-80.

44. Sarkisyan M.S. Chemical-toxicological study of metamizole in urine / M.S. Sarkisyan, D.S. Lazaryan // Toxicological Bulletin. - 2012. - No1. - P. 44-48.

45. Sivolap Yu.P., Savchenkov V.A., Mishnaevsky A.L. Multiple damage to internal organs in opium addiction. //Journal of Neurology and Psychiatry. - 2000. - No 6. - P. 64-65.

46.Sorokina V.V. Genetic markers in the forensic medical assessment of cases of acute and chronic intoxication with opium narcotics // Forensic medical expert. - 2010. - No. - P. 19-21.

47. Forensic medical examination of lethal poisoning by narcotic substances /O.V. Krieger, S.V. Mogutov, S.V. Butovsky, et al. //Forensic medical examination. - 2001. - No. - P. 9.

48. Temerdashev A.Z., Grigoriev A.M., Rybalchenko I.V. Evolution of new narcotic drugs and methods for their determination // Journal of Analytical Chemistry. 2014. Vol. 69. No 9. P. 899.

49. Tolstolutskiy V.Yu., Possibilities of Increasing the Efficiency of Various Mathematical Model Options for Determining the Timing of Death.-V kn.yp.4-Izhevsk: Ekspertiza,1995.-P.27-32.

50. Tomilin V.V., Pygolkin Yu.I. The state of scientific research in forensic medicine and the introduction of research results into expert practice// Forensic Medicine. Expert.-1997.-Vol.40, No2.-P.8-10.

51. Chromova A.M., Alexandrova L.G., Zabusov Yu.T. Features of the histostructure of internal organs in acute and chronic poisoning with opiates materials of the 14th Plenum of the All-Russian Society of Forensic Medical Workers (June 17-18, 1999) - M.,1999.-P.50-51.

52. Shvyreva O.V. Socio-hygienic aspects of drug poisoning in forensic medical examination: abstract of diss.... cand. med. sciences. - Novosibirsk, 2005.-20 p.

53. Shigeev S.V. Forensic Medical Assessment of Toxicological Data on Deaths from Opiate Poisoning //Bulletin of the Peoples' Friendship University of Russia. Series: Medicine. 2007. No. P. 63-68.

54. Shigeev S.V. Forensic Medical Examination of Opiate Intoxication: Abstract of Diss.... Doctor of Medical Sciences. - M., 2007. -48 p.

55. Shigeev S.V., Zharov V.V. Forensic Medical Diagnostic Value of Morphine Content in Blood and Urine // Sud_med.ekspert. - 2006. - No. - P. 39-42.

56. Shigeev S.V., Zhuk Yu.M. Alcohol - a risk factor for fatal opiate poisoning // Problems of Expertise in Medicine. 2005. Vol. 5. No 3 (19). P. 30-33.

57. Shigeev S.V. Toxicological characteristics of opiate poisoning // Problems of Expertise in Medicine. 2005. Vol. 5. No 1 (17). P. 25-26.

58. Yakubov Kh.Kh., Piriyeva L.V., Iskandarov A.I. Determination of the toxicokinetics of household, industrial poisons and medicinal products. //1th Regional Conference of the International Association of Forensic Toxicologists for the CIS and Central Asian Countries "Problems of Forensic and Clinical Toxicology." - Tashkent, 2015. - P. 62-64.

59. Piriyeva L.V., Yakubov Kh.Kh., Abdukarimov B.A. Toxicometric assessment of poisoning with caustic poisons. //1th Regional Conference of the

International Association of Forensic Toxicologists for the CIS and Central Asian Countries "Problems of Forensic and Clinical Toxicology." - Tashkent, 2015. - P. 110-111.

60. Ahmadi B, Arab P, Zahedi MJ, Shafieipour S, Drossman DA, Banivaheb G. Prevalence of narcotic intestinal syndrome in opioid abusers in iran. Middle East J. Dig Dis. 2014 Oct;6 (4):208-13.

61. Amadasi A, Mastroluca L, Marasciuolo L, Caligara M, Sironi L, Gentile G, Zoja R. Death due to acute tetrachloroethylene intoxication in a chronic abuser. Int J Legal Med. 2015 Jan 21.

62. A retrospective analysis of antidepressant poisonings in the emergency department: 11 years of experience /P.Unverir et al. //Hum. Exper. Toxicol. - 2006. - Vol. 25. - P. 605-612.

63. Balhara Y.P., Mathur S. Bhang - beyond the scope of the narcotic drugs and psychotropic substances act. Lung India. October 31, 2014:431-2.

64.Chavant F, Boucher A, Le Boisselier R, Deheul S, Debruyne D. New synthetic drugs in addictovigilance. 2015 Mar-Apr;70 (2):179-89.

65.Compton WM, Boyle M, WargoE. Prescription Opioid Abuse: Problems and Responses. 2015 Apr 11. pii: S0091-7435 (15) 00103-6.

66. Dargan P., Wood D. Novel recreational drugs and "Legal Highs" over the last five years // J. Med. Toxicol. earlyonlinepublications.

67. Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B, Green JL. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med. 2015 Jan 15;372 (3):241-8.

Delaveris GJ, Hoff-Olsen P, Rogde S. Unnatural deaths among drug users: pathological findings and illicit drug abuse stigmata. Am J Forensic Med Pathol. 2015 Mar;36 (1):44-8

69. Häkkinen M, Vuori E, Ojanperä I. Prescription opioid abuse based on representative postmortem toxicology. Forensic Sci Int. 2014 Oct 24;245C:121-125.

70. Harun A, Agrawal Y. The Use of Fall Risk Increasing Drugs (FRIDs) in Patients with Dizziness Presenting to a Neurology Clinic. 2015 Mar 30.

71. Jalilov F., Zoxidova A., Zokirova G., Tojiyev M., Jalilova F. Development of a thermodesorption surface ionization spectroscope method for analyzing some antidepressants. // The 50th Annual Meeting of TIAFT Joint Meeting of JSLM & TIAFT. Hamamatsu (Japan). - 2012.

72. Intravenous maintenance of opiates in a cohort of injection drug addicts. P.Sendi, M.Hoffmann, H.C.Bucher et all //Drug and Alcohol Dependence - 2003. Vol. 69 (2). - P. 183-188.

73. Mohapatra S, Rath N. Appraisal of the Narcotic Drugs and Psychotropic Substances (Amendment) Act, 2014. Asian J Psychiatr. 2015 Mar 14. pii: S1876-2018 (15) 00041-6.

74. Nickerson JW, Attaran A. The Commission on Narcotic Drugs' attempt to restrict ketamine. 2015 Mar 7;385 (9971):e19.

75. O'Malley P A. Opioid abuse, misuse, and death: the promises and limitations of drug barrier technology now and in the future. 2015 May-June;29 (3):139-42

76. ÖNeill DF, Webb Thomas C. Less is more: limiting narcotic prescription quantities for common orthopedic procedures. PhysSportsmed. 2014 Nov;42 (4):100-5.

77. Pawlik E, Mahler H, Hartung B, Plässer G, Daldrup T. Drug-induced death: Adulterants from cocaine preparations in lung tissue and blood. Forensic Sci Int. 2015 Apr;249:294-303.

78. Sušnjara IM, Gojanović MD, Vodopija D, Smoljanović A. Difficulties in recording drug abuse mortality. Cent Eur J Public Health. 2014 Dec;22 (4):288-90.

79. Tanaka N, Kinoshita H, Kuse A, Takatsu M, Jamal M, Kumihashi M, Nagasaki Y, Asano M, Ueno Y, Ameno K. Forensic toxicological implications of pleural effusion; an autopsy case of drug overdose. Soud Lek. 2012 Summer;57 (3):48-50.

80. Travasso C. Government findings suggest that counterfeit and substandard drugs in India may be a smaller problem than claimed. BMJ. 2014 Jan 7;348:g60.

81.Fucci N, Pascali VL. Acute morphine and cocaine-related death after trimethoprim-adulterated cocaine abuse. Ann Clin Lab Sci. 2014 Fall;44 (4):499-501.

82. Sigvaldason K, Ingvarsson T, Thordardottir S, Kristinsson J, Karason S. Injecting drug abuse: survival after intensive care and forensic toxicology reports at death. Laeknabladid. 2014 Oct;100 (10):515-9. Icelandic.

83. Yakubov Kh.Kh., Piriyeva L.V., Iskandarov A.I. Determination of the toxicokinetics of household, industrial poisons and medicinal products. //1th Regional Conference of the International Association of Forensic Toxicologists for the CIS and Central Asian Countries "Problems of Forensic and Clinical Toxicology." - Tashkent, 2015. - P. 62-64.

84. Piriyeva L.V., Yakubov Kh.Kh., Abdukarimov B.A. Toxicometric assessment of poisoning with caustic poisons. //1th Regional Conference of the International Association of Forensic Toxicologists for the CIS and Central Asian Countries "Problems of Forensic and Clinical Toxicology." - Tashkent, 2015. - P. 110-111.

85. TursunkhodjaevaSh.U., Ibragimova M.M. Chemical-toxicological analysis of morphine by the method of thermodesorption surface-ionization spectroscopy. //1th Regional Conference of the International Association of Forensic Toxicologists for the CIS and Central Asian Countries "Problems of Forensic and Clinical Toxicology." - Tashkent, 2015. - P. 135-136.

86. Tursunkhodzhaeva Sh.U. Morphological changes of live acute drug poisoning. //1th Regional Conference of the International Association of Forensic Toxicologists for the CIS and Central Asian Countries "Problems of Forensic and Clinical Toxicology." - Tashkent, 2015. - P. 137-138.

87. Tursunkhojayeva Sh.U., Murodov N.Kh. Pathogenetic mechanisms of development of dystrophic liver changes in chronic drug poisoning. //III International Scientific and Practical Conference "Prospects for the Development of Science and Education." - Moscow, 2016. - P. 165-169.

88. Yakubov Kh.Kh., Iskandarov A.I., Kodirov K.U. Expert diagnosis of death in acute poisoning with narcotic substances. //Tashkent Medical Academy Bulletin. - Тошкент, 2016. - No. - P. 112-114.