

**Proceedings of the 1st and the 2nd
Japanese and Russian International
Conference on Socially Significant
Human Diseases: Medical,
Environmental, and Technical
Problems, and these Solutions**

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HOKUTO SOCIAL MEDICAL CORPORATION

Academic collaboration with Far Eastern federal University

The Hokuto Social Medical Corporation was the first Japanese medical organization to begin operations in Russia, at the Hokuto Imaging Diagnostic Center in Vladivostok, on 28 May 2013. The center was started by a consortium of four members who seek to bring Japanese medical care to the Russian Far East: the Stroitel Sanatorium in suburban Vladivostok; Akira Co., Ltd. and PJJ Co., Ltd., established to arrange for the treatment of Russian patients in Japan; and the Hokuto Social Medical Corporation.



The center has two primary goals: (1) to promote secondary preventive medicine by early and precise diagnosis of disease by imaging modalities before it becomes symptomatic, thus preventing disease progression; and (2) to reappraise the diagnosis of the previously diagnosed diseases and the treatment plans. Since June 2013 to May 2015 the center had treated more than 12,000 patients, indicating a high demand for these medical services in the Russian Far East region. Taking the regional and innovative rationale of the center, academic collaboration and human exchange in social and medical field of science is indispensable to fully realize the aims of the center. This scientific conference will be of great importance for the success of our projects including a center of rehabilitation medicine in this year.

It is vital that we ensure the continuation and future growth of the conference. Just at this moment, preemptive medicine was one of the most important theme at The 29th General Assembly of The Japan Medical Congress in Kyoto. It would be worthwhile to bear this concept in mind as we promote our academic collaborations and strive for continued success.

May 2015

Hajime Kamada

President, Hokuto Social Medical Corporation

Editor's preface



This is the first volume of the Proceedings of the Japanese–Russian International Conference series promoted by the Hokuto Social Medical Corporation (HSMC), Hokuto Hospital (HH), Obihiro City, Japan, and by the Far Eastern Federal University (FEFU), Vladivostok, Russia. The first conference was held on 22 May 2014, and the second on 27–28 May 2015, both at the conference hall of the FEFU. This series was jointly established by Hajime Kamada, MD, President of HSMC Hokuto Hospital, and Professor Valery N. Bagryantsev, MD, PhD, Chairman of Bioengineering Science, FEFU. After the first meeting, the conference series was named the Japanese–Russian International Conference on Medical, Environmental and Technical Problems in Socially Significant Human Diseases and their Solutions (JRIC-SSD), as proposed by Professor Bagryantsev.

The contents of this book are scientific abstracts and reports by researchers at FEFU staffs and HSMC Hokuto Hospital members. These cover a wide range of topics in social and medical sciences, divided into four sections, 1, New Theories and Devices 2, Regional Socio-Economic Analysis and Interpretations, 3, Epidemiology and Public Health, 4, Functional Foods, and 5, Therapy. It is hoped that readers of this book will gain from the novel ideas presented herein, be inspired by the passion of the authors, and be invigorated by the spirit of socio-medical science. These contributions remind us that science is intriguing and without borders.

I should apologize all blemish in this book that are my fault as the chief editor. However, I sincerely thank all contributors, especially the President Kamada, and the Professor Bagryantsev as I could put myself promoting this project. Furthermore, I also express sincere appreciation to Dr Svetolana Denisova, General Director, Hokuto Healthcare Corporation, Vladivostok, who created and managed initial steps of this collaboration. Finally, I thank to all of our staffs in HSMC HH, especially to Mr Masao Oshima and Mr Alexander Selivanov, on Russian and International Projects, and Mrs Kazuka Onishi, Secretary, all who worked for this publication.

May 2015

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SECTION 1

New Theories and Devices

Chapter 1

LINEAR MATHEMATICAL MODEL OF DIAGNOSTIC PROCESS

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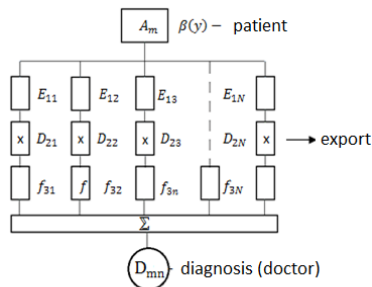
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Abstract. Improving disease diagnostics using mathematical modeling has potential in health-care research [1,2,3]. We attempted to develop a principal linear mathematical model to reduce the influence of subjective and variable factors on screening processes and disease diagnosis. A mathematical analysis of the possibility to improve the current diagnostic process was conducted for modern schemes of laboratory and instrumental diagnostics. Recommendations are given for developing prospective mathematical models and systems for carrying out diagnostic medical, biological research.

Keywords: mathematical model of laboratory and instrumental diagnostics, diagnostic process algorithms.

To understand the diagnostic process, we suggest a linear scheme that represents patient investigation realized in parallel in several directions.



Equation (1) then follows:

$$D_{mn} = \sum_{k=1}^N D_{2k} \int \beta(y) f_k(y-k) dy = \int \beta(y) [\sum_{k=1}^N D_{2k} f_k(y-k)] dy \quad (1)$$

In this mathematical interpretation, the diagnosis D_{mn} is a response of a linear diagnostic system with “preliminary” diagnosis D_{2k} as the general signal received from a patient $A_m(\beta(y))$:

$$\Psi_m(y) = \sum_{k=1}^N D_{2k} f_k(y-k). \quad (2)$$

Here the model $f_k(y-k)$ is the transfer function of a signal with index k .

The task of system optimization of the linear signal processing from patient $A_m(\beta(y))$ is in the choice of the preliminary diagnoses D_{2k} , which supply the optimal (true) connection with the investigated function $\beta(y)$ describing the patient state A_m .

This task can mathematically be reduced to a feedback task (synthesis) of expression (1).

For example, consider the special case of all transfer functions of all channels being equal: i.e., $f_k(y) = f(y)$.

If measured data (physical, chemical, microbiological, or other) come to the multichannel system in the form of a signal from different analytes as function $\beta(y)$, then a complex signal is registered in the output of channel k .

$$a_k = \int \beta(y)_k (y-k) dy. \quad (3)$$

One can choose a Kotelnikov series member for a linear instrumental research (radio, electronic, or other) function system:

$$f_k(y-k) = \frac{\sin \pi(y-k)}{\pi(y-k)}. \quad (4)$$

That is, the main contribution to coefficient a_k is made by the values $\beta(y)$ concentrated in proximity to the point $y = k$.

However, function (4) has a value significantly away (by > 20%) from the central maximum $y = k$.

Therefore, it is not possible to state the local diagnosis using only expression (3).

Information about value E_{1k} is distributed among the great number of preliminary diagnoses. To extract reliable information, one should conduct joint signal processing from all channels (3).

$$D_n = \sum_{k=1}^N \alpha_{mk} D_{2k}. \quad (5)$$

The optimal function describing a diagnosis is therefore formally determined as the sum of local diagnoses in expression (5).

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Chapter 2

**AUTONOMOUS DEVICE
FOR CONJUNCTIVAL MICROSCOPY**

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The major aim of this creation of a device that films the microvascular bed of the bulbar conjunctiva, for use in both medical and preventive treatment facilities and in cases of emergency, extraordinary situations, and battle. It must also be minimally invasive to the patient.

The device contains an optical system, including a video camera with a transfer system, an illuminator containing two white-light-emitting diodes that is rigidly mounted on the video camera in such a way that the direction of the luminous flux makes an angle of not less than 20° to the optical axes of the system, and a system for the control, registration, and analysis of the images realized on the ECM base, as well as a communication unit to support the dynamic feedback between the optical system and the controlling system.

The system receives images from the video camera in real time and screens them on the monitoring device. The software analyzes the acuity, intensity, and contrast of each image and adjusts the camera transfer characteristics to use its dynamic range to the maximum effect. Each image is subjected to Fourier transform analysis and wavelet analysis to evaluate its frequency and contrast characteristics. Those meeting the required characteristics (input into the parameter unit) are saved to the memory or onto the computer hard drive. This is followed by the activation of the announcing wireless channel units that cause audible signals. The saved images and the preprocessing results can be displayed in a separate monitor window. This process is repeated until the number of images specified in the parameter block has been recorded. The announcing unit signal then stops, which signals to the operator to stop

filming the conjunctiva. The set of recorded images is then analyzed in detail in the morphological analysis unit, and the results are saved and displayed. The process of recording and analyzing the medical images takes no more than 2 minutes.

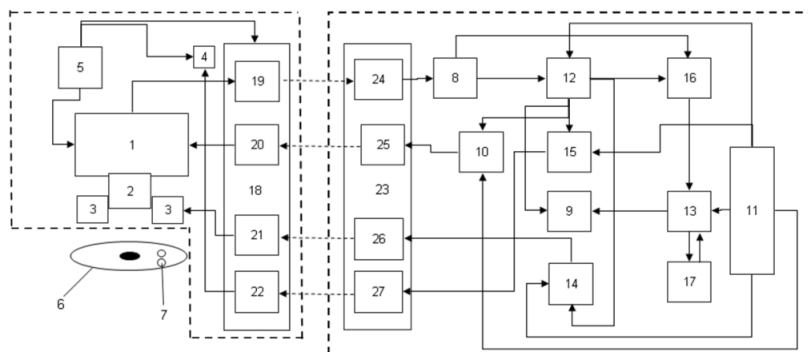


Fig. 1 Principal Diagram of the Device

1, Video camera; 2, image transfer system; 3, illuminator; 4, announcing unit; 5, power unit; 6, eye conjunctiva; 7, light spot; 8, display buffer; 9, video display unit; 10, unit for controlling the camera transferring characteristics; 11, parameter input unit; 12, preanalysis unit; 13, morphological analysis unit; 14, illumination-intensity controlling unit; 15, recorded frame counter; 16, image recording unit; 17, unit for recording the results of the morphological analysis; 18, unit for the optical system wireless communications; 19, first element for image wireless translation; 20, first element for image characteristic wireless translation; 21, first element for the wireless control of the illumination characteristics; 22, first element for the wireless announcing channel; 23, unit for the analysis of wireless communications; 24, second element for image wireless translation; 25, second element for image characteristic wireless translation; 26, second element for the wireless control of the illumination characteristics; 27, second element for the wireless announcing channel.

Functional units 8–17 and 23–27 of the device are contained within a hardware–software complex on a notebook base, while units 1–7 and 18–22 are located on the mobile device itself.

Chapter 3

**MATHEMATICAL MODELS OF DIAGNOSTICS
USING ACTIVE WAVE DEVICES**

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Abstract: Algorithms and mathematical models are proposed to improve medical screening and early disease diagnosis by active wave medical devices. They are shown to be able to improve the existing systems and technologies used in medical “interoscopy”. Recommendations are also provided for creating new cybernetic developments and prospective devices for veterinary, medical, and biological research.

Key words: mathematical models of diagnostics, active wave devices for interoscopy.

Wave devices are appliances that use the properties of elastic and electromagnetic waves to determine the body’s inner structures (body interoscopy). Active wave devices employ echo sounding to analyze wave reflections from inhomogeneities in the body; examples include ultrasonic research (USR) and electromagnetic sonars [1,2].

Medical interoscopy devices include radio technical systems that use antenna and signal synthesis theory, wide-band lines matching, or other radio-physics techniques [3,4].

Inhomogeneities in the body that reflect detectable signals include bone structures and pathological formations such as stones in the kidney or gallbladder and tumors.

The task of restoring in the physical plane arises when we find a continuous intensity function of signals reflected from different areas of inhomogeneity, measured in separate areas of space (i.e., multiple similar objects). Let us suppose that the experimentally measured function $\Phi(u)$ is connected to a searched (or unknown) function $V(\zeta)$ by an integral operator:

$$\Phi(u) = \int_a^b \sigma(u, \zeta) V(\zeta) d\zeta, \quad (1)$$

where $\sigma(u, \zeta)$ denotes a nucleus of integral equation, u denotes a generalized angular coordinate set in the interval $[c, d]$ ($c \leq u \leq d$), and a and b denote the goal (stone) sizes ($a \leq \zeta \leq b$).

The second type of restoring task can employ the $\Phi(\zeta)$ antenna direction diagram calculation according to the experimentally measured power concentration of the reflected signal $W(u)$:

$$W(u) = \int_a^u \sigma(\zeta) \Phi(\zeta) d\zeta, \quad (2)$$

where $\sigma(\zeta)$, $a \leq \zeta \leq b$ are set parameters.

Operators (1) and (2) are linear. The solution of these integral equations refers to incorrect tasks of mathematical physics, which lead any device made to employ these restoring tasks to be unstable to both external and internal interferences.

Comparison of both mathematical models shows that measurement should be conducted by different methods. In the first case, the function $\Phi(u)$, measured at discrete points, can be interpolated to be continuous, and integral equation (1) can be solved in one of the known ways.

In task 2 the unknown function $\Phi(\zeta)$ is determined in the area $[a, u]$. Therefore,

$$\Phi(\zeta) = \sigma^{-1}(u) \frac{d}{du} W(u).$$

The last algorithm is not possible in principle, [because the function $W(u)$ is known only at discrete points. This leads to differences between devices using this algorithm and those that employ the other algorithm. Let us consider the main mathematical problems facing the

development and realization of medical devices working according to algorithm (1) using USR as an example.

The experimentally measured function of the response from an inner inhomogeneity (e.g., a stone) can be either complex or real. A complex function should occur when the amplitude and phase of the signal reflected from an inhomogeneity are measured simultaneously. A real function occurs when only the amplitude is analyzed. Most modern devices (e.g., USR) analyze only the reflected signal amplitude $|\Phi(u)|$.

In this respect the incorrectness of the solution of integral equation (1) is expressed not only in the instability of the derived solutions $V_n(\zeta)$ ($n = 1, 2, 3, \dots$). That is, a great number of inhomogeneity (stone) types and configurations can be put to one and the same reflection function $\Phi(u)$.

In practice, the correct diagnosis (i.e., the choice of inhomogeneity type) depends on the subjective choice of the doctor (or operator), which depends on the individual's qualifications, experience, and ability to use the device software. Image analysis time and other factors can also affect the decision. To decrease the influence of subjective judgments requires mathematical processing of the derived experimental images $|\Phi(u)|$. One such method follows.

We create a matrix of the most likely types of inhomogeneity standards $|V_n(\zeta)|$, calculate the integral (1), and find functions $\Phi_m(u)$ that correspond to types $V_m(\zeta)$.

We make up a matrix of the images $(|\Phi_m(u)|)$ that correspond to standard inhomogeneities $V_m(\zeta)$. Note that integration using formula (1) for a smooth kernel $\sigma(u, \zeta)$ is unambiguous and correct. That is why the created matrices can be the basis (foundation) for the whole class of USR devices working in accordance with the described algorithm.

As the integral equation solution is incorrect and gives many solutions $V_m(\zeta)$ that correspond to various inhomogeneity types, one must choose the only optimal solution $V_{\text{opt}}(\zeta)$ (i.e., the solution which corresponds to the probable correct description of the true form of the inhomogeneity).

Let us consider one of the probable algorithms of mean square error minimization σ_m^2 between (recommended) standard images $|\Phi_m(u)|$ and those experimentally measured $\Phi(u)$:

$$\sigma_m^2 = \int_{-u_0}^{u_1} |\Phi_m(u) - \Phi(u)|^2 du. \quad (3)$$

When chosen in accordance to mean square criterion (3), the function $\Phi(u)$ can be found insufficient for investigation of the detailed structure of an inhomogeneity. Detailed estimation requires other parameters such as the minimax proximity criterion.

$$\varepsilon_m(u) = \max |\Phi_m(u) - \Phi(u)| \quad (4)$$

Specific mathematical algorithms of error minimization (3) and (4) could be developed for similar tasks of the mathematical function. These might be, for example, used in antenna synthesis theory, analyzing the structures of underground mineral deposits, and other radio prospecting tasks.

Suggested algorithms for medical diagnostics can be used to develop new programs for processing the images from interoscopy devices.

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SECTION 2

Regional Socio-Economic Analysis and Interpretations

Chapter 4

**INFLUENCE OF ECOLOGICAL AND HYGIENE FACTORS
ON THE PREVALENCE OF ONCOLOGICAL DISEASES
IN THE PRIMORYE TERRITORY**

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Abstract

The prevalence of oncological pathologies under the multifactorial environmental influences during the period of 2000 —2013 was evaluated based on the system analysis method. The ecological dependence of oncologic disease prevalence in the Primorye Territory was attributed to the complex inhabitation environmental effect, characterized by the complicated mechanism. A direct correlation was identified between the zones of ecological stress and the levels of morbidity in the population associated with lung and stomach cancer, skin neoplasms, intestinal cancer, and oncological urological pathology (bladder and kidney cancer). The extent of factor modules impact on the oncological pathology features of different localization forms had a multidirectional character. The obtained results were used to develop a comprehensive regional program named “Oncology”.

Key words: systems analysis, prevalence, oncological disease, ecological and hygiene module factors

Introduction

Malignant neoplasms are one of the major health-care issues in both developed and developing countries, and ten million new cases and more than six million deaths are registered globally every year. According to a rough estimate by the World Health Organization, 25 million people suffered malignant neoplasms throughout the world in 2000, one million were newly diagnosed and seven million died. The

number of new cases of cancer is estimated to increase up to 27 million by 2030 and patients living with cancer will be 75 million [13].

The discontinuity in the prevalence of oncological diseases in different regions and the changes in morbidity that occur with population migration conclusively confirm the relationship between cancer development and the ecological aspects of human existence [1].

As reported by the International Agency for Research on Cancer, 85% of human tumors can be attributed to the influence of environmental factors [13]. More in-depth investigations of these ecological factors are required to understand the epidemiology of cancer because the factors contributing to oncogenic risk in a population are closely related to the ecological conditions of different climatic and geographical zones [4,9,10,15,17]. Studies devoted to the issue of malignant neoplasms show that the main etiopathogenetic and epidemiological elements that define the prevalence of malignant neoplasms are environmental conditions [2,5,6]. Some authors have demonstrated that 70%–90% of human tumors are related to lifestyle characteristics and to the impact of carcinogenic factors in the environment [11,12,16]. Malignant neoplasms are considered to be an indicators of the health status of a population, and are highly dependent on the quality of environmental conditions, so any increase in cancer morbidity is often considered to indicate ecological situations (problems) in a region [3,4,7]. The dependence of the prevalence and frequency of malignant neoplasms on the anthropogenic load and environmental quality has been confirmed in domestic and foreign studies [1,2,9,13,14,15,16].

The incidence rate of malignant neoplasms has increased in Russia in recent years and decades. This attributed to unfavorable population processes, the ecological condition of the environment, and social and economic situations (problems) [1]. Unfavorable conditions for the development of oncological diseases have been created in the Primorye Territory, an outlying region of Russia, in the last 15–20 years, in terms of its natural and climatic features and specific ecological and social problems. In the period from 2000 to 2013, the intensive ratios of oncological diseases for both sexes increased from 2720.76 per 100,000 cases to 3834.21 per 100.000 cases , where the ratio increased by 30.1%. It must be noted that the oncological pathology levels increased in all the cities and regions of the Primorye Territory, and the incidence in the city area was higher than in the rural areas, probably because of higher

environmental pollution in the city area. An investigation of environmental quality in the Primorye Territory showed unfavorable natural, climatic, ecological, and social parameters for the environment, increasing the risk of malignant neoplasm [4].

Study objective

The purpose of this study was a systems analysis of the dependence of the prevalence of oncological disease on the ecological and hygiene conditions in the Primorye Region.

Results and Discussions

In assessing whether the prevalence of oncological diseases depends on the ecological situation, we identified relationships between the levels of all forms of oncological disease and the status of the ecological zones. A direct correlation was identified between zones of ecological stress and the level of population morbidity in terms of lung and stomach cancer, skin neoplasms, intestinal cancer, and oncological urological pathologies (bladder and kidney cancer). However, no correlation was identified between the environment and the prevalence of diseases such as breast, ovarian, and cervical cancer. The prevalence of these diseases must be attributable to other factors.

The prevalence of oncological pathology increases in zones of critical ecological stress, where coal mining and chemical industries, ship repair enterprises, construction and machine building industries are located, and in regions of intensive use of chemical substance in agricultural development. These are present in cities and towns such as Artem, Spassk, Vladivostok, Ussuriysk, and Dalnegorsk, and regions such as Spasskiy, Dalnegorskiy, Kavalerovski, Shkotovski, Khohorolskiy, Chernigovski, and Khankayskiy. In these cities, towns, and regions are situated more than half of all enterprises that produce first- and second-grade harmful conditions. The levels of harmful substances in the air, soil, and water of these areas often exceed 10-fold the maximum allowable concentrations.

Our next objective was to analyze the factor complexes (modules) that affect oncological pathologies [8]. For this purpose, grouped factors were weighted against the oncological pathology indices of newly diagnosed morbidity, sickness, and mortality. The following facts were identified with this analysis. Sickness and mortality were most often attributed to environmental factors, which influenced the general

indices of oncological pathology in the Primorye Territory. Newly diagnosed morbidity was most strongly influenced by the hygiene module (in the cities, this module influenced 52.8% of morbidity, 54.0% of sickness, and 55.3% of mortality) and the social and economic module influenced the structure of general indices.

The most common nosological entity, lung cancer, was predominantly affected by the hygiene module in all three categories (morbidity, sickness, and mortality), and this dependence was the same in the cities, regional areas, and all over the Primorye Territory. The influence of the social and economic module on cancer prevalence was smaller, and the influence of the ecological module was much smaller.

Colon cancer morbidity was predominantly attributed to the factors of the hygiene and social and economic modules, and the influence of these two modules was approximately equal in the cities. The prevalence of skin neoplasms and bladder cancer was similarly dependent on environment influences in the cities and all over the Primorye Territory.

We also defined the influence of environmental factors on hemoblastosis. The factors of the social and economic module were most influential on the population morbidity, illness, and mortality in the cities (on 46.3% of morbidity, 34.2% of illness, and 35.1% of mortality). The factors of the hygiene module were less influential. However, the influence of the ecological module was high, and was almost equal in the cities, rural regions, and all over the Primorye Territory. The defined factors of the environment influence on hemoblastosis show some features of this oncological pathology prevalence in the Primorye Territory. This phenomenon requires further specialized study.

It must be noted that the module factors relating to anthropogenic impact and the module factors characterizing the social infrastructure were more influential on the oncological pathology of malignant neoplasms and their prevalence in the cities, whereas in the region areas, the ecological module factors were more influential. From the results of this analysis, it can be inferred that different environmental factors influence the levels of oncological morbidity differently throughout the Primorye Territory. The factors of hygiene module predominantly influence the level of oncological morbidity in cities such as Arsenyev, Vladivostok, Spassk-Dalniy, and Dalnegorsk, and in the Nadezhdinskiy, Kavalerovskiy, Khankaiskiy, and Chernigovskiy regions. The factors of the social and economic module defined the levels of oncological

pathology in cities such as Dalnegorsk, Artem, Partizansk, and Ussuriysk, and in regions such as Olginskiy, Partizanskiy, Mikhailovskiy, and Khorolskiy. Ecological factors influenced the prevalence of oncological pathology in Nakhodka, Dalnegorsk, Dalnerechensk, Lesozavodsk, and BolshoyKamen, and in the Terneyskiy and Krasnoarmeiskiy regions. Therefore, using the systems approach to analyze these multifactorial influences, the cause and effect relationships were defined in the system “environmental conditions–oncopathology”. Defining the influence factor modules of the environmental conditions as a multisystem negative effect on the rates of oncopathological morbidity, illness, and mortality in the Primorye Territory, and their quantitative evaluation allows us to determine appropriate medical and preventative interventions. Understanding the main trends in the prevalence of malignant neoplasms in the Primorye Territory in response to environmental factors allows us to predict the oncological morbidity in specific periods in the future, and was the basis for the Primorye Territory program “Oncology”.

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Chapter 5

**PREVALENCE AND ORIGIN OF HIV-1 RESISTANCE
IN PROMORSKY KRAI, RUSSIA**

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Variants of drug-resistant human immunodeficiency virus (HIV) have become increasingly widespread; genotyping of HIV isolate is an important method for identifying the mutations associated with drug resistance. This article addresses the prevalence of different HIV subtypes and circulatory recombinant forms and describes the molecular structure of drug-resistant HIV-1.

Key words: HIV, drug resistance, sequencing, subtype.

The prevalence of drug-resistant HIV strains, which is associated with high replication rates of HIV and the high incidence of replication errors, is one of the reasons that antiviral therapies are ineffective in some patients [1]. Molecular genetic methods are therefore necessary to select therapies that are tailored to individual patients.

Research objective

To analyze the prevalence of mutations in drug-resistant protease genes and HIV-1 reverse transcriptase strains, and to examine the prevalence of HIV-1 subtypes.

Materials and methods

Genetic data were obtained by sequence analysis of HIV RNA in 61 patients. Mutation resistance was determined by virological and/or immunological response in patients.

Results

A survey of genetic variants of HIV-1 among HIV-infected patients living continuously in the territory of Primorski Krai revealed a prevalence of HIV-1 subtype B of 49% (39 individuals), and a prevalence of subtypes A and C of 21% and 23%, respectively. In addition, we detected a low prevalence of circulating recombinant forms: 1 occurrence each of CRF01_AE/A and B/A, and 2 occurrences of CRF02_AG.

All patients were identified mutation polymorphism in the gene for protease and reverse transcriptase. The prevalence of mutations was: minor mutations in 20 (33%) patients, mutations of the protease inhibitor gene in 3 (5%) patients, mutations of the reverse protease inhibitor gene in 34 (56%) patients, and no mutations in primary or secondary resistance genes in 26 (43%) patients. Conclusions: The dominant HIV subtype among the examined patients was subtype B, along with several circulating recombinant forms; these results confirm previously reported data [2]. It is known that CRF01 occurs in Southeast Asia and is the prevailing form in Thailand [3]. Recombination of the genomes could occur outside of the Primorsky territory, and its territory; the patient could be infected already generated a recombinant form or be infected simultaneously/sequentially these genetic variants. Subtype CRF02_AG is widespread in African countries, Kazakhstan, and in the territories of Russia–Altai and Novosibirsk.

Primary resistance mutations to protease inhibitors identified in individual cases, which may be due to insufficiently large period of use of these drugs. Dominated by drug-resistance mutations to reverse transcriptase inhibitors as more commonly prescribed drugs HAART. It is necessary to conduct further research on the analysis of the prevalence of drug resistance of HIV-1 to HAART [4].

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Chapter 6

**PHILOSOPHICAL FOUNDATIONS
OF SOCIALLY SIGNIFICANT DISEASES
AND IMPLICATIONS FOR INTERVENTION**

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Abstract

This paper addresses key problems raised by the prevalence of socially significant diseases (SSDs) in modern society. We examine fundamental social–philosophical issues raised by SSDs, in an effort to systematize and understand the social dimensions of problems associated with SSDs in today’s global civilization.

Keywords: social problems, socially significant diseases, social risks

In the mid-20th century, a new concept of *social diseases* appeared in social–philosophical discourse, according to which diseases arise in the context of socio-economic conditions, and that resulting impacts on society must be addressed in terms of social and human security [1]. In modern society, the problem of *socially significant diseases* (SSDs) comprises both social and medical dimensions. A fundamental assertion of modern social–philosophical discourse is that social well-being is a critical existential issue in today’s world, and well-known contemporary social philosophers (e.g., Beck, Giddens, and Luhmann) are addressing the essential nature of modern global civilization in this from this viewpoint [1]. Giddens considers today’s societal problems to be intensifying as a consequence of scientific and technological progress [2].

Social problems and vectors of social change are integral components of life in every society, and they define the social space in which we live. In modern sociology, the analysis and understanding of social problems represents a growing field of investigation. Recently,

Yamrotsis and Notsella presented a powerful model to address the world's social problems [3], and their conceptual model serves as a basis for understanding the social problems associated with SSDs. According to Yamrotsis and Notsella, the concept of social problems can be applied both to the social processes and the conditions that most people perceive as undesirable and/or threatening to basic society values, such as social order, justice, and the stability of social institutions. Publically accepted agreements—formalized as laws and regulations, or informally represented by public opinion—can be perceived as social problems as well, if they are contrary to the interests of specific social or socially defined demographic groups. Societal problems can arise due to a sense of collective guilt, caused by public neglect and a lack of awareness regarding specific social phenomena and conditions, thus resulting in negative impacts on some sectors of society.

The concept of *social problems* and their consequences can be applied to a wide variety of phenomena. The impacts of social problems can be devastating if adequate preventive measures are not undertaken to preclude or eliminate the consequences of those events, or if the problems are not suitably evaluated by society or by individual communities as unsatisfactory. In addition, the main characteristic feature of social problems is the possibility, or at least the potential possibility, of their inherent solvability. Generally, the state is responsible for solving social problems, and within this framework one can single out specific dimensions of various phenomena for which some aspect or aspects are social; i.e., those with an identifiable social origin or which exhibit a real or potential threat to societal values or interests. The identification of the nature of the social problem is thus necessary for its resolution. The SSDs, which are sometimes thought of as socially dangerous in some way, are one of the most prominent social problems facing modern society. The spread of SSDs threatens the core values and fabric of society by threatening human life itself. Moreover, SSDs negatively impact demographic and economic stability. The SSDs that are most prominent, and that receive the most recognition, are those that pose a threat to other individuals [2, 3], as such diseases require the formulation of numerous legal and social norms. In general, the state and society are responsible for both the spread and the containment of SSDs, and in this respect, a sense of collective responsibility is a primary motivator for the state to reduce the risks of SSDs.

An understanding of the social problems associated with SSDs provides the basis for current social–philosophical discourse, which often revolves around societal transformations from a modern to postmodern civilization—in other words, the transformation from an industrial to a post-industrial society. Such a transformation is associated with the transition from social norms based on certainty and rationality, which are inherent in modernity, to those based on relativity and uncertainty, which are inherent in a postmodern society. Within the realm of social–philosophical discourse, postmodernism arose at the end of the 20th century, associated mainly with the works of Foucault and Lyotard [4]. A postmodern view of relativism has become a critical attitude not only within the sciences, but also in the context of social values and normative structures.

We here define some characteristic features of contemporary society that are critical for the ensuing analysis of SSDs, in the context of social processes using postmodern terminology. We first address the characteristics of social structures in postmodern society. Social classes in postmodern society are related to capitalistic economic structures, limiting their importance as essential elements of social order. To replace the social class structure with a more complex and heterogeneous organizational foundation requires an inter-weaving of economic, gender-related, age-related, and cultural factors. As compared with traditional social structures, the social structure of a postmodern society is more fragmented and more differentiated.

Moreover, factors related to health and health behavior become critical structure-forming components of a postmodern society, and the presence or absence of certain kinds of diseases becomes a basis for social differentiation. Relevant diseases include both socially acceptable and socially unacceptable diseases. For example, diseases of the musculoskeletal system are acceptable in society, and people with such disabilities form a separate social stratum for which an entire infrastructure has been created and developed. Diseases associated in the public mind with socially unacceptable behaviors affect the social structures of modern society. For example, HIV has become a structure-forming factor, and HIV-infected individuals have been relegated to independent social communities in modern society.

Beck identified an important characteristic feature of modern society, which he referred to in his famous work *Risk Society* [5]; this feature is the presence of imminent danger, as the differentiation of

secure and insecure zones in the modern world are increasingly blurred. Modern society is characterized by certain kinds of social risks, which, according to Beck, are typified by the Chernobyl meltdown. The Chernobyl disaster and its sequelae represented the end of an era in which we could distance ourselves from one another, as the essential feature of radioactive contamination is worldwide connectivity. Borders can provide protection from poverty, but not from the dangers of atomic contamination. Therefore, the cultural and political forces behind the Chernobyl disaster symbolize the underpinnings of modern society [6].

Threats to life and well-being posed by the dangers of social conflicts create heavy existential social burdens, which have serious short- and long-term consequences. To eliminate the constraints imposed by one's social identity, and to allow opportunities to make decisions that secure the individual a place in the social structure by virtue of his or her merits alone, a new model of ascriptive variety must emerge in society. In contrast to the system of caste and class, an ascriptive model develops without regard to financial status, fear, or traditional norms; such a model represents the highest stage of social development in a postmodern society. Technological developments have redefined the risks and hazards associated with SSDs, such that they are unevenly distributed globally, and as the borders of nation states are permeable and transparent to SSDs, the prevalence of fears and risks associated with SSDs have created new social-psychological community structures. Social movements are now founded in the context of a global community, and measures of the success of current policies can only be assessed at national and international levels.

The recognition of the new and evolving context of modern society has led contemporary social analysts to consider post-industrial society to be a risk society, with the risks associated with SSDs constituting one of the basic risks of life in modern society. It should be emphasized that, within the inclusive list of behaviors resulting in SSDs, many are determined by institutional factors, including the lack of preventive strategies for disease, generally inadequate preventive medicine, the lack of satisfactory educational systems, and problems related to the legal dimensions of SSDs.

A consideration of SSDs in the context of risk prevention requires a review and reinforcement of policies supporting social workers, as social workers play a central role in the management and mitigation of risk in a risk society. Thus, in addition to medicine, the fields of social

work and psychology should play key roles in developing adequate preventive strategies in the battle against SSDs [8].

The national and global scope of social problems related to SSDs must be addressed, particularly in the case of socially dangerous diseases, which often result in stigmatization and discrimination. Stigmatization associated with SSDs has a hugely negative impact, not only on individuals, but also on the community in general. At the individual level, stigmatization affects self-esteem, causing despair, low self-worth, and depression. Often, social stigmas associated with an illness cause a negative emotional feedback loop to arise in an individual: For instance, if a man identifies himself as an outlaw, the social consequences are exclusion from normative social structures, and a deterrent response by law enforcement, manifesting society's moral assumption that good people live according to the law. Social stigmatization can devalue a person and challenge his or her social identity. This destabilizes that person's emotional well-being, promoting actions that are deemed socially unacceptable [9].

At a societal level, stigmatization undermines efforts at disease prevention, and more subtle and diffuse forms of behavior may replace those that are more obvious or severe. Despite new and more supportive forms of social control, new social interaction models describe downward trajectories in individuals with diseases, especially socially dangerous diseases. For example, Foucault describes trajectories leading to insanity, involving alienation, control, and exclusion; such trajectories are prevalent in postmodern society [10].

Modern social–philosophical discourse on the problems and risks associated with SSDs in a postmodern society offers avenues for addressing these problems. For example, Giddens describes a neoliberal project that develops software policies as a response to a risk society. Regulation, rather than risk management, is the hallmark of such a neoliberal social policy. Giddens' neoliberal project reduces the risks associated with the modern world by taking social work and psychological care as a central tenet. Developers of Such neoliberal projects claim that any intervention to reduce risk, including interventions associated with SSDs, should include social work as a main component of the solution. Social workers help individuals maximize self-improvement as a means of solving problems; thus, goals include building new relationships between clients and resource systems, developing interactions between individuals and resource systems that improve the

efficiency of such interactions, and developing policies that improve social assistance and change. State policies under these circumstances must be linked to providing basic social protection, and the accompanying social services should be associated with citizens' activities and the development of personal responsibility.

Thus, we conclude that the best way to prevent SSDs is to establish state-specific legal and social institutions that strengthen the capacity of citizens to take individual responsibility for their physical and social well-being; however, such personal achievements should not reduce the responsibility of states to create programs that appropriately manage risk.

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SECTION 3

Epidemiology and Public Health

Chapter 7

**SCREENING METHODS
FOR PRECANCEROUS CONDITIONS**

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The feasibility of combining modern innovative techniques and research methods (liquid-based cytology, automated cytological scanning, PCR detection of human papilloma virus) for the diagnostic screening of precancerous cervical pathologies is demonstrated.

Keywords: screening, cervical cancer, Pap test, human papillomavirus.

The screening methods used to monitor human health incorporate recent developments not only in medicine, but also in interdisciplinary areas of the fundamental sciences, especially the biomedical sciences. The main objective of these methods is to identify disease in the early, clinically asymptomatic stages of its course, to allow an accurate clinical examination and the prompt identification of the appropriate measures for the management of the disease. The use of screening to determine the pathological changes in the body that can presage malignant neoplasms is especially relevant. According to World Health Organization data, screening for malignant neoplasms in the lung, breast, stomach, colon, and uterine cervix is reasonable in Russia, and accords with the high level of morbidity in the population. The effectiveness of the screening methods used has already been demonstrated in the cases of mammography for breast cancer, the fecal occult blood test for colon pathologies, and cytological screening for pathologies of the uterine cervix.

Special attention must be paid to uterine cervical cancer because it is the third most common malignant neoplasm and the fourth most common cause of death from oncological disease in women throughout the world. The development of extensive modern technologies has made it possible to improve traditional diagnostic methods, which provided grounds for using cytological screening of cervical smears as a screening method. These methods allow the condition of cervical cells to be

monitored in the stage of the pathological process preceding the formation of a malignant neoplasm. Unfortunately, ~30% of cervical cancers are not detected in time, due to improper sampling, uninformative samples generated when preanalytical (preparatory) processing procedures are violated, and the subjective assessment of the cells' condition by cytologists [4]. The application of new material-processing technologies at the preanalytical stage has considerably improved the effectiveness of screening methods. These methods include liquid-based cytology for cell suspensions obtained from liquid biomaterials; rapid cell fixation on different types of slides (prefixing "in volume mass" or liquid suspension fixation); purification and separation of liquid samples using cell gradient centrifugation or filtration centrifugation; and suspension treatments before the cells are placed onto slides, which include the differential lysis of specific cell types, deproteinization, solution purification to remove cell debris, and the correction of the cell concentration in the final volume. The manipulations performed with these techniques allow thin-film preparations to be made that can be used for diagnosis not only with traditional cytological screening of cervical material (Papanicolaou staining method) using optical microscopy, but also with an automated cytological scanning system. This system consists of three components: automatic sample scanning, database formatting, and the ranking of cellular elements according to the signs of atypia (presence and degree) with a software package and the expertise of a professional cytologist. Thin-layer preparations treated with these techniques can be used for additional research to narrow the diagnosis, including the direct, immune, or cytochemical identification of the virus.

In this context, an important discovery of the role of human papillomavirus (HPV) in the genesis of cervical cancer, which was recognized by the Nobel committee, suggest that viral testing is warranted in patients in whom dysplastic processes have been identified in the epithelium of the uterine cervix. According to randomized controlled and cohort studies of HPV, testing for the virus is more sensitive than cytological screening in detecting precancerous changes in the uterine cervix and invasive cancer (cervical intraepithelial neoplasia II and III, adenocarcinoma *in situ*, invasive cancer) [2,3]. However, the detection of HPV and the identification of the viral genotype using molecular methods (PCR) as part of the screening process have a limitation that these also detect transient infections, especially in young women [1]. In the USA

and Europe, testing for high-risk HPV (HR-HPV) is recommended for women with atypical squamous cells of undetermined significance (ASCUS) and is performed in addition to cervical cytological screening in patients aged over 30 years. However, the combination of cervical screening with HPV testing may provide unmatched results. Therefore, when a result HR-HPV test for the imperceptible cervical diseases is negative, the necessity/number of colposcopies can be reduced, which will increase the cost-effectiveness of screening. The assignment of patients with ASCUS and positive HR-HPV results to a specific high-risk group using this method will circumvent unnecessary appointments for colposcopy and also intensive interventions for women who do not need them. The results of the multicenter ATHENA (Addressing the Need for Advanced HPV Diagnostics) study in the United States, in which more than 47,000 women participated, showed that the genotype of the virus must be determined and the condition of the precancerous uterine cervix established when the combined screening method is used. The application of cervical cytological screening using modern material-processing technologies at the preanalytical stage and HPV testing, with the definition of the virus type, can significantly improve the diagnosis of precancerous pathological changes in the uterine cervix. The combination of these methods allows the organization of medical practices to be optimized and guarantees rational and economically effective cervical screening.

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Chapter 8

**CLINICAL INFLUENZA CAUSED BY
DIFFERENT VIRAL SEROTYPES**

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Hospital records (n = 531) for the last six years (2009–2014) were analyzed. The diagnoses of influenza were confirmed with nasopharyngeal swabs using real-time polymerase chain reaction. The etiological analysis showed that influenza A (H1N1) pdm09 occurred in 261 patients, accounting for 46.5% of patients; influenza A (H1N1) was diagnosed in 148 patients (26.4%); influenza A (H3N2) in 102 patients (18.2%); and influenza B in 50 patients (8.9 %). Influenza A (H1N1) pdm09 caused disease that was clinically more severe than seasonal influenza.

Influenza is one of the most widespread diseases in the world. According to World Health Organization data, influenza and other respiratory viral infections make up 60%–70% of the total world morbidity.

Objective

Our objective was to examine the clinical features of influenza, according to the viral serotype.

Materials and methods

The hospital records of 531 influenza patients treated at the Infectious Disease Department of the Primorye Territory Regional Clinical Hospital #2 in the past 6 years (2009–2014) were analyzed retrospectively.

Results

All patients were divided into four groups: patients with influenza A (H1N1) pdm09 (group 1, n = 261); or those with seasonal influenza: influenza A (H1N1) (group 2, n = 148), influenza A (H3N2) (group 3, n =

102), or influenza B (group 4, n = 50). All influenza diagnoses were confirmed with the polymerase chain reaction. Patient age ranged from 21 to 64 years (mean, 26.9), and the major proportion (36.3%) of patients were 20–29 years old. The sample population contained 51.2% women and 48.8% men. Moderate disease severity prevailed (87.4%), but 12.6% of patients experienced severe disease. The disease started abruptly, with pyrexia, headache, and muscle and joint pain in 89% of patients. The patients with influenza A (H1N1) pdm09 were febrile (39.5 ± 0.04 °C), and their fever lasted for 5.0 ± 0.9 days on average, whereas those with seasonal influenza were subfebrile (37.5 ± 0.06 °C), and their fever lasted for 2.5 ± 0.6 days. Catarrhal syndrome affected 74% of group 1 patients, 29% of group 2 patients, 34% of group 3 patients, and 7% of group 4 patients on the first day of the disease. Among the complications reported, sinusitis was most frequently observed (16.2%), pneumonia was recorded in 9% of patients, and myocarditis was a complication in 0.5% of patients. The average duration of hospitalization in group 1 was 7.5 ± 0.5 days, but only 5.5 ± 0.4 days in groups 2, 3, and 4 ($p < 0.05$). As antiviral therapies, 7.2% of patients received oseltamivir, 76.1% received umifenovir, and 16.7% received symptomatic treatment. The mortality rate was 1.6%, and only patients infected with influenza A (H1N1) pdm09 died.

Conclusion

Infection with the highly pathogenic influenza A (H1N1) pdm09 virus was characterized by more severe disease progression than the seasonal disease.

Chapter 9

**MARKERS OF INTERFERON AND CELLULAR IMMUNITY
IN MEN WITH RECURRENT GENITAL HERPES
AND CHLAMYDIAL CO-INFECTION**

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In this study, we sought to identify markers of interferon and cellular immunity in patients with genital herpes and *Chlamydia trachomatis* co-infection. The cell profile of herpetic urethritis was characterized by an increased frequency of lymphocytes expressing a marker of early activation (CD25⁺) among normal cells expressing HLA-DR, and by an increased frequency of apoptotic-capable cells. These profiles are associated with abnormal activation, switching from early to late activation, together with a functional defect of T cell immunity. Patients with herpetic urethritis co-infected with *C. trachomatis* showed a significant increase in the frequency of CD3⁺CD25⁺ cells and increases in the markers of later negative activation against lower phagocytosis. These results are consistent with chronic cell activation, and priming of T lymphocytes for the induction and activation of apoptosis in these patients. Co-infected patients also exhibited relative interferon- γ insufficiency.

Key words: genital herpes, *C. trachomatis*, immune status, interferon.

Genital herpes is associated with significant morbidity. In 20th century, it was classified as one of the 70 most common diseases, and is associated with major social and healthcare problems. About 1 billion people, about 1/6th of the world's population, are infected with herpes simplex virus (HSV) type 2 [9]. In the Russian Federation, the incidence of HSV infection was estimated to be 18.4 per 100,000 people in 2011 [1]. Many studies have focused on the clinical manifestations and treatment of genital herpes, as well as its adverse effects on the female

reproductive system. However, there is limited information regarding the role of HSV as an etiological factor in genitourinary system diseases in men. The deleterious effects of HSV on various organs are widely accepted, and its role in carcinogenesis and secondary infertility is well established. For example, studies examining the effects of HSV and human cytomegalovirus using semen revealed that HSV was more common in idiopathic infertility, and was associated with reductions in active mobile spermatozoa and the proportion of morphologically normal germ cells [8]. Thus, there is no doubt that HSV modifies the immune responses of humans to various pathogens [7]. Studies of sexually transmitted infections showed that genital herpes was commonly associated with chlamydial infection owing to the common epidemiologic characteristics of the causative pathogens [5, 2]. In addition, persistent asymptomatic infections, particularly *Chlamidia trachomatis*, may trigger immune responses and delay hypersensitivity reactions, key factors in male infertility [9]. Immunologic homeostasis is especially important in the persistence of viral and bacterial urogenital infections. HSV type 2 is associated with disturbed interferon (IFN) and cytokine activities [4]. Some qualitative changes were found in the course of infection because the causative pathogens could substantially change their pathogenic properties through interactions with other pathogens. Therefore, clinically, patients with co-infection acquire certain characteristics, which vary considerably from those of patients infected with a single pathogen. Immune disorders are more apparent in co-infected patients and are less susceptible to traditional treatment regimens, reducing the therapy's effectiveness, activating pathogenic microflora, changing the causative pathogen's properties, and increasing the risk of super-infection.

Purpose

To evaluate the immunologic features and measure the concentrations of IFN α and IFN γ in men with recurrent genital herpes and chlamydial co-infection.

Materials and methods

We analyzed venous blood samples from 30 men aged 20–45 years with chronic urethritis. There were 13 (43.3%) patients with chronic recurrent herpetic urethritis and 17 (56.7%) with chronic urethritis with a mixed bacterial and viral etiology (genital herpes co-infected with *C. trachomatis*). We also analyzed venous blood samples from 30 healthy

male volunteers as a control group. Lymphocyte phenotyping and markers of phagocytosis were assessed by flow cytometry using monoclonal antibodies from BD Biosciences (USA). The serum IFN γ concentration was measured using specific reagents from R&D Diagnostics Inc. (USA). The serum IFN α concentration was measured using an enzyme-linked immunosorbent assay (sandwich method) from Vector Best (Russia) in accordance with the manufacturer's instructions. The results were recorded using an enzyme immunoassay analyzer (Multiscan, Finland). The cytokine concentrations (in pg/ml) were calculated by drawing a calibration curve using computer software. Data were analyzed descriptively using Student's *t* test with Biostat software version X.

Results and discussion

Cells expressing CD markers and their combinations were identified in the major lymphocyte populations (i.e. T, B, natural killer [NK], and natural killer T [NKT] cells) using markers of positive (CD25 and HLA-DR) and negative (CD95) lymphocyte activation. We focused on two lymphocyte subpopulations, namely T helper cells (CD3⁺CD4⁺ cells) and cytotoxic T cells (CD3⁺CD8⁺ cells). The results of these analyses showed that the cellular profile in patients with chronic urethritis was significantly different from that in the control group (Table 1).

Table 1. Immunophenotyping of immunocompetent cells, immunoglobulin levels, and phagocytosis indices in patients with chronic urethritis and in healthy men

Indicators	Patients with urethritis			Healthy men n=30
		HSV-1.2 n=13	HSV-1.2 C. trachomatis n=17	
CD3 ⁺ CD19 ⁺	%	69.23±2.51	70.82±1.52	70.30±2.15
	cell/10 ⁹ /L.	1.01±0.07	1.33±0.12	1.42±0.14
CD3 ⁺ CD4 ⁺	%	42.00±1.87	38.06±2.05**	47.50±2.20
	cell/10 ⁹ /L.	0.64±0,03	0.69±0.07	0.96±0.10
CD3 ⁺ CD8 ⁺	%	25.08±0,89	28.70±1,98	31.10±1.90
	cell/10 ⁹ /L.	0.39±0.02	0.53±0.06	0.62±0.11
CD3 ⁻ CD19 ⁺	%	13.62±1.18	11.88±0.81*	14.92±1.26
	cell/10 ⁹ /L.	0.20±0.02	0.22±0.02	0.30±0.05

CD3 ⁺ 16 ⁺ 56 ⁺	%	13.40±1.98	14.15±1.32	13.85±0.80
	cell/10 ⁹ /L.	0.22±0.05	0.25±0.02	0.28±0.07
CD3 ⁺ CD16 ⁺ 56 ⁺	%	5.19±1.27	5.26±1.33	3.44±0.06
	cell/10 ⁹ /L.	0.08±0.02	0.09±0.02	0.07±0.02
CD25 ⁺	%	13.69±1.28***	16.23±1.19***	9.12±0.82
	cell/10 ⁹ /L.	0.21±0.02	0.31±0.04	0.20±0.07
CD3 ⁺ CD25 ⁺	%	7.53±0.92 p ₁₋₂ <0.05	10.30±0.86***	6.15±0.70
	cell/10 ⁹ /L.	0.11±0.01 p ₁₋₂ <0.05	0.20±0.03*	0.14±0.04
CD95 ⁺	%	23.38±2.30*	23.77±2.67*	16.20±1.20
	cell/10 ⁹ /L.	0.36±0.03	0.42±0.05	0.32±0.06
CD3 ⁺ CD95 ⁺	%	15.36±1.81**	16.35±2.34***	7.14±0.12
	cell/10 ⁹ /L.	0.23±0.02*	0.30±0.05*	0.15±0.03
HLA-DR ⁺	%	15.37±1.30	14.62±0.74	13.90±0.86
	cell/10 ⁹ /L.	0.24±0.02	0.27±0.02	0.28±0.06
CD3 ⁺ HLA-DR ⁺	%	2.26±0.28	2.74±0.28	4.00±0.62
	cell/10 ⁹ /L.	0.03±0.002	0.05±0.008	0.09±0.02
CD4 ⁺ /CD8 ⁺		1.69±0.09	1.55±0.16	1.55±0.15
phagocytic index	%	66.31±4.55	64.18±4.62*	76.3±1.4
phagocytic number		3.80±0.38	3.62±0.41*	4.80±0.20

Notes: *p < 0.05, **p < 0.01, and ***p < 0.001 versus the control group; p₁₋₂, p-value for the comparison between the two groups of patients with urethritis.

We observed several common patterns and characteristics in the distributions of the examined factors in men with herpetic urethritis and men with genital herpes co-infected with *C. trachomatis*. In particular, there were no significant differences in the frequencies of CD3⁺CD4⁺ cells and CD3⁺CD8⁺ cells between these two groups. However, the frequency of CD3⁺CD8⁺ cells was significantly lower in the co-infected group than in the control group. The ratio of CD3⁺CD4⁺ cells to CD3⁺CD8⁺ was not significantly different between both groups. The IRI value did not extend beyond the reference range in any subject.

By analyzing the expression of markers of lymphocyte activation, we observed significant differences in the frequencies of cells expressing these markers among the study groups. In particular, the frequency of

CD25⁺ lymphocytes was increased in 6 (46.15%) patients with herpetic urethritis and in 12 (70.58%) patients with herpetic urethritis co-infected with *C. trachomatis*. In addition, we found a significant increase in the frequency of CD3⁺CD25⁺ cells in patients with herpetic urethritis co-infected with *C. trachomatis* and an increase in the frequency of CD3⁺CD95⁺ cells (a marker for negative lymphocytes activation) in both groups of patients with urethritis. However, the frequency of cells expressing HLA-DR was not significantly different between patients with chronic urethritis and the control group. These results indicate that the lymphocytes have switched from early activation to late activation, which may reflect a functional defect of T cell immunity. There were no differences in the frequencies of NK cells or CD3⁺CD19⁺CD56⁺ cells, a minor cell population, or of NKT cells. The phagocytic analysis showed that the quantitative indices of phagocytosis were significantly lower in patients with herpes co-infected with *C. trachomatis* than in the control group.

The serum IFN γ concentration was significantly elevated in patients with herpetic urethritis compared with the control group ($p < 0.01$), but not in patients with herpes co-infected with *C. trachomatis* (Table 2). These results suggest that patients may have a relative shortage of IFN γ , consistent with a functional defect in T helper 1 lymphocytes.

Table 2. Serum cytokine profile in patients with chronic urethritis and healthy men

Indicators	Patients with urethritis		Healthy men n=30
	HSV-1.2 n=13	HSV-1.2 <i>C. trachomatis</i> n=17	
IFN γ	27.24 \pm 6.06** ($p_{1-2} < 0.01$)	10.05 \pm 0.65	12.52 \pm 0.63
IFN α	10.8 \pm 0.9*	14.92 \pm 1.82**	4.6 \pm 0.4

Notes * $p < 0.05$ and ** $p < 0.01$ versus the control group; p_{1-2} , p-value for the comparison between the two groups of patients with urethritis.

It was previously reported that a local deficit in IFN γ is associated with a reduction in T helper 1 lymphocytes and impaired macrophage function in patients with chlamydial urethritis or chlamydial urethritis co-infected with other pathogens [6]. IFN γ plays a key role in the eradication of *C. trachomatis*, and low IFN γ concentrations allow persistent infection.

The serum IFN α concentrations were significantly greater in both groups of patients with chronic urethritis than in the control group, consistent with a compensatory reaction to viral infection and viral and bacterial co-infection.

Conclusions

The cell profile of patients with herpetic urethritis is characterized by an increased frequency of lymphocytes expressing the marker of early activation (CD25⁺) despite a normal frequency of cells expressing HLA-DR, and an increased frequency of cells with apoptotic potential. These results are indicative of abnormal activation of immune cells, switching from early activation to late activation, together with functional defects in T cell immunity. Herpetic urethritis co-infected with *C. trachomatis* was associated with a significant increase in the frequency of CD3⁺CD25⁺ cells, increased expression of markers of later negative lymphocyte activation, reduced phagocytosis indices, and relative IFN γ deficiency. These findings are consistent with chronic cellular activation and priming of T lymphocytes for the induction and activation of apoptosis in patients with herpetic urethritis co-infected with *C. trachomatis*.

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Chapter 10

**PREDICTION OF HCV-THERAPY EFFECTIVENESS
IN HCV/HIV-CO-INFECTED PATIENTS**

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Hepatitis C virus (HCV) is the most common cause of liver disease in HIV-infected patients. A combined analysis of baseline characteristics and data: such as sex, age, HCV genotype, HCV and HIV viral load, stage of fibrosis, HIV stage, clinical and biochemical blood test, cytokine levels, etc, will allow a more accurate prediction of the results of HCV-treatment in these patients, significantly increase therapeutic efficiency and optimize treatments for co-infected patients, as well as improve existing methods of treatment. We investigated criteria for effectiveness of HCV therapy in HIV-infected patients and created a predictive scale for its outcome on the basis of monitoring of the clinical, laboratory and cytokine parameters. Because the scale is based on evaluation of the initial data, it can predict the probability of sustained virological response prior to the commencement of HCV treatment in HCV/HIV co-infected patients.

Key words: HCV/HIV co-infection, HCV treatment, predicting scale

Introduction

Chronic infection by hepatitis C virus (HCV), contracted as a result of blood-to-blood transmission, is the most common cause of liver disease in HIV-infected patients. Among 35 million HIV-infected individuals, up to 20% (7 million) are also infected with HCV. In the HIV population of the Russian Federation, the incidence of HCV is 60% to 70%, and most of these patients have a history of intravenous drug abuse [2, 3]. The last decade was marked by the introduction of highly active antiretroviral therapy (HAART) into clinical practice; HAART has reduced mortality

and the incidence of opportunistic infections, and has significantly improved the life expectancy and quality of life of HIV patients [5]. Under these conditions, chronic HCV has become one of the leading causes of death among HIV-infected patients [8].

The principal approaches to HCV treatment under conditions of co-HIV-infection are the same as those for mono-HCV-infection. However, the necessity of HAART for the HIV-treatment, as well as the treatment and prevention of opportunistic infections, determines the features of an integrated therapeutic approach for management and treatment of co-infected patients. The positive response probability of HCV treatment is largely determined by virological characteristics (e.g., genotype and viral load) as well as a variety of clinical and immunological criteria, all of which significantly influence therapeutic success.

Despite numerous studies, the mechanisms of immunological damage by HIV infection are still not entirely clear [4, 9]. The results of systemic cytokine profile examination] of HCV/HIV patients are often contradictory. In the future, a combined analysis of baseline characteristics and data such as listed at the beginning of article will allow more accurate predictions of the efficacy of HCV treatment in HIV-patients, significantly increase therapeutic efficiency and also optimize treatment protocols for co-infected patients.

The goal of our study was to investigate criteria for measuring the effectiveness of HCV therapies in co-infected HIV patients and to create a predictive scale for assessing therapeutic outcomes according to clinical, laboratory, and cytokine profile parameters.

Materials and methods

We examined 289 HCV/HIV co-infected patients treated for 48 weeks with PEG-IFN alfa-2a and ribavirin. We determined the cytokine status (IL-2, 4, 18, IFN α , γ , and antibodies to IFN α) and analyzed case records retrospectively for 120 of these patients. Patients were followed at an AIDS center in Vladivostok during the period 2006–2014 [7].

The patients were divided into two groups according to results of the HCV therapy. The first group consisted of co-infected patients who had achieved a sustained virological response (SVR) at 24 weeks after the end of the therapy; the second group consisted of non-responders, i.e., patients who had not achieved SVR. Statistical analyses were conducted using SPSS IBM Statistics v. 22.

Results

The study group concluded 182 males (63%) and 107 females (37%). The average age of all individuals was 35.0 ± 4.7 years. Of the study group, 49% presented stage 4A HIV infection, 51.2% received HAART, and 59.5% achieved SVR.

We used neural network analysis to select predictors that were statistically associated with SVR achievement [1, 6]. The predictors were classified according to the average value of the indices in the group that had achieved SVR. For the regression model, we selected a categorical regression with optimal scaling (CATREG). This model was chosen because, in addition to the standardized regression coefficients, the analysis yields “importance coefficients”, with the absolute values of the coefficients being proportional to the importance of the regression coefficients; therefore, they are proportional to the degree of contribution of each predictor (i.e., the “weight”) to the dependent variable (SVR achievement). The coefficients used to create the scale were selected according to the importance of their weighted values. A score was then calculated for each of the predictors in the regression model to create the scale (Table 1).

Table 1. Evaluation scale for the sustained virological response (SVR) prognosing

Predictor	Value	Score
Age	>40 years	8.5
HCV viral load	$\geq 500\ 000$ IU/ml	0.15
IL-2 before treatment	> 4.3 pg/ml	2.5
IL-4 before treatment	> 0.75 pg/ml	30
IFN α before treatment	> 6.85 pg/ml	44
IFN γ before treatment	> 10.5 pg/ml	17
IL-18 before treatment	> 1230 pg/ml	0.3
Anti-IFN α -antibodies before treatment	> 0.44 pg/ml	2
HIV stage	4A–4B	0.3
HIV viral load	>150 cop/ml	0.07
CD4+ T-lymphocytes before treatment	>518	0.5
HAART	No	0.08
Stage of fibrosis	F3–F4	2.5
ALT	$\geq 2N$ U/L	1.3

*A total score of less than 50 is indicative of a high risk of HCV-treatment inefficiency.

Next, to determine the threshold for the total score, a theoretical probability range was defined for which SVR had not been achieved. According to results of the regression analysis, the range of scores was constrained to the interval of 0–50. Thus, we determined a minimum indicative score (50) for which successful HCV-therapy was practically not observed, and this score was adopted as a preliminary threshold. The theoretical values of threshold points were tested by binary logistic regression, in which only one categorized predictor was used, i.e., the total score of the patient (≤ 50 or > 50); the dependent variable was SVR. This regression model based on the received program data is carried out within the forecast 83.3% (coefficient of determination, $R^2 = 0.644$) [1].

Discussion

Predicting the effectiveness of various treatments is a promising area of medical science, regardless of field or specificity. Numerous new factors that directly or indirectly affect the outcomes of treatments are being examined to evaluate the effectiveness of chronic hepatitis C therapy, and the number of promising predictors is increasing daily. With regard to HCV infection, treatment is increasingly individualized, especially in cases of HCV/HIV co-infection; this individualization complicates the assessment of therapeutic effectiveness and thus the development of strategies for treating HCV/HIV patients.

In this study, we developed a scale that allows patients to be easily placed into one of two groups: those who are non-responsive to therapy, and those who have achieved SVR. The scale should be useful for clinicians, who must make decisions about patient management and care. The scale, based on an initial evaluation of patient status, allows to predict probability of SVR achievement in HCV/HIV co-infected patients before HCV-treatment start.

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Chapter 11

**DEVELOPMENT OF ALGORITHMS
FOR THE DETECTION OF BLADDER CANCER
CAUSED BY URINARY SCHISTOSOMIASIS**

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Relevance.

Urinary schistosomiasis (US) is common in humans infected with *Schistosoma haematobium*, and is associated with an increased risk of bladder cancer (BC). BC typically affects young, employable people and usually occurs within 10–20 years after primary US (El-Harvey M.A. et al., 2000; Lopatkin N.A. et al., 2010). US is endemic to many regions, especially parts of Africa and the Middle East. Owing to global migration, cases of US have also been reported in East-Asian and European residents (Xue K. et al., 2011; Honeycutt J. et al., 2014).

In most endemic countries, schistosomiasis-associated BC (shBC) is detected during the invasive growth stage in over 80% of cases, and requires radical surgical treatment and pelvic exenteration. Histologically, squamous BC is associated with a low degree of dissemination (Ploeg M. et al., 2009). The World Health Organization recommends that patients who present with gross hematuria should be prescribed standard doses of antiparasitic drugs (e.g. praziquantel) (El-Harvey M.A. et al., 2000; Salem H.K. et al., 2012). However, continued follow-up of patients with newly diagnosed US is a concern because, once gross hematuria is resolved following oral therapy, patients with US are often discharged from medical care and are not routinely followed up (Shokeir A.A., 2004). Unfortunately, many patients with shBC are hospitalized within a few months to 1 year because of repeated gross hematuria caused by cancer invasion into muscle tissue.

Purpose of the study.

To improve the diagnosis and treatment of shBC.

Materials and methods.

We analyzed 56 patients who originally presented with hematuria and were treated at our medical clinic in the Province of Benguela (Angola) between 2009 and 2012. The duration of gross hematuria since the first manifestation ranged from 3 weeks to 12 months. All patients were black, with 49 (87.5%) rural and 7 (12.5%) urban residents. Due to the last group admission, the patients used untreated water for domestic purposes.

The patients were divided into two subgroups (A and B) according to the diagnostic and treatment approaches. Group A comprised 35 patients, of which 19 (54.3%) were women (mean age 37 years) and 16 (45.7%) were men (mean age 35 years). This group of patients was analyzed retrospectively. This group of patients were initially prescribed praziquantel (40 mg/kg) and antibiotics. They were discharged once the gross hematuria had resolved. Patients with recurrent hematuria were prescribed praziquantel and underwent routine urological examinations: cytological examination of urine sediment (CEUS), ultrasonography of the pelvic organs and abdomen, arB due to indications, cystoscopy followed by biopsy and excretory urography, and computed tomography. Following the detection of BC, the patients were referred for specialized treatment.

Group B was a prospective group of 21 patients, of which 13 (61.9%) were women (mean age 31 years) and 8 (38.1%) were men (mean age 28 years). This group of patients received a modified diagnostic and treatment plan, as follows. First, the patients were directed to an urologist in the outpatient department of the regional hospital and then sent to a day-ward, where a wide range of diagnostic procedures were performed, including CEUS, ultrasonography, cystoscopy with biopsy of the bladder mucosa, and trans-urethral resection and biopsy (TURB), as indicated.

Results.

BC was confirmed in the majority of patients ($n = 30$) in group A, and surgery was performed in all of these patients. The pathology reports revealed the presence of squamous cell carcinoma with schistosome eggs in the inflamed mucous membranous areas in all of the remote tissue

preparations that were assessed. In 1 (2.86%) patient with pT2N0M0 BC, we performed open segmental resection of the bladder. In 28 (80%) patients, we ascertained locally advanced and disseminated BC, which was classified as pT3-4N0-3M0-1. Among these 28 patients, 23 (82.1%) underwent radical cystectomy with urinary diversion, while 5 (17.9%) underwent ureterocutaneostomy owing to advanced malignancy. One (2.9%) patient with gross hematuria was referred to us from the maternity hospital at week 37 of pregnancy. After the diagnostic examinations, the patient underwent cesarean section and cystectomy with a neobladder using a modification of the Mainz–Pouch II method. The patient and her baby were discharged from the hospital in a satisfactory condition. Malignancies affecting the female or male genitalia were found in 5 (14.3%) patients in group A.

In 4 (19.0%) patients in group B, cystoscopy revealed proliferative changes in the urothelium caused by the schistosomes. All of the patients underwent TURB on the same day as cytoscopy. The histological report confirmed the presence of schistosome eggs, but there was no evidence of urothelial malignant lesions. BC was confirmed in 12 (57.1%) with a grade of pT1-2N0M0 and required surgery. These patients underwent TURB ($n = 5$, 41.7%) or open segmental resection of the bladder ($n = 7$, 58.3%) including three pregnant women (week 35–39 of pregnancy). In 1 (4.8%) patient, macrohematuria occurred because of reflux caused by kidney stones. Prostate cancer had spread to the bladder in 2 (9.5%) patients.

Schistosome eggs were detected by CEUS in 28.2% of patients. Based on the results of ULS, shBC was suspected in 46.8% of patients. In 63.5% of patients, cystoscopy revealed urothelial neoplastic changes or gross (> 1.5 cm in diameter) proliferative changes of the bladder mucosa, caused by schistosomal activity.

Conclusions.

Using standard diagnostic methods, we observed a low sensitivity for and a long delay in the diagnosis of BC in group A. Only a combination of different diagnostic modalities (i.e. morphologic, radiologic, and endoscopic methods) together with diagnostic surgery in a ward setting was sufficient to reach an accurate diagnosis and treat these patients in a timely manner.

The early detection of urothelial tumors allowed us to perform organ-sparing surgery in patients in group B. We believe this approach

provided better quality of life and more favorable outcomes for these patients compared with the standard approach.

Prophylactic treatment of US with praziquantel did not help to prevent shBC. It is important that healthcare providers in regions endemic for US to organize their diagnostic strategies and implement a stepwise approach to ensuring patients with hematuria are quickly referred for comprehensive examinations in an outpatient center. Such centers should be equipped with the necessary diagnostic equipment and experienced staff.

The diagnostic and treatment strategy for patients with US should include cystoscopy and, if indicated, TURB. This approach allows us to identify shBC at an early stage. Early surgery because of gross urothelial changes in patients with US is justified for preventing the development of squamous cell BC. We need a landmark clinical marker to help identify patients with early US symptoms because of the high risk of developing shBC within 10–20 years of the initial US infection.

Chapter 12

**GENDER FEATURES BASED ON A COMPARATIVE
ANALYSIS OF CLINICAL RESEARCH
OF HIV-INFECTED MEN AND WOMEN**

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Studies of gender distribution in the cumulative number of patients with HIV infection in the Primorsky region show that men dominate, although the number of women is increasing. The nature of opportunistic infections is comparable for both sexes. However, significant differences were observed when *Candida esophagitis* and herpes infection. Numerous studies have been conducted on gender, HIV, therapeutic strategies, and their relationships. Over time, these studies will contribute to improved health advice for women.

Key words: HIV infection, gender, opportunistic infections

The total number of HIV-infected individuals in Russia exceeded 800 thousand in 2014 [1]. Approximately 80% of new HIV cases in Russia are in persons 18–29 years old [1, 2]. Cases of HIV infection are registered with the Russian Federation. According to regional statistics, on 31 December 2014, 7732 HIV-infected persons resided in Primorsky territory, and the prevalence of HIV-infected inhabitants in the territory was 398.9 per 100,000 population. An analysis of the incidence and prevalence of the HIV-infected population of Primorsky during the 3-year period from 2011 to 2014 indicates that the number of HIV-infected individuals is increasing. All medical facilities in the region provide screening and examination for HIV, and treatment of patients with HIV. It is known that access to medical care and the opportunity to use is largely determined by gender roles in society. Women face numerous challenges and barriers related to their health and well-being. For

example, many women suffer from domestic violence, and their economic and social position is, on average, lower than that of men, and they are often economically dependent on a partner. Many women are raising children alone, and their time, money, and effort go first and foremost to the health of their children, and their own health care needs are often neglected. These problems may prevent women from visiting a doctor. Since it is known that many diseases occur in men and women with different frequencies, and that symptoms, complications, and manifestations of diseases vary with gender, it is likely that HIV infection in women presents itself differently than in men. Relations between the sexes and the likelihood of infection with opportunistic pathogens may be due to anatomical or biochemical data (for example, the pH of the vagina) or neuroendocrine differences between man and woman. In the course of HIV infection may play a role complex hormonal interactions and related sex differences in the clinical manifestations of opportunistic infections [3].

Purpose of the study

To study gender features on the results of the comparative analysis of follow-up of HIV-infected men and women

Materials and method

We analyzed the dispensary treatment cards of 117 patients with a diagnosis of HIV infection. The total sample was divided into two groups based on gender and stage of the disease. The first group consisted of 59 men with stage III–IV (late) HIV infection. The second group consisted of 48 women at similar stages of infection.

Results of the study

An analysis of the cumulative number of patients with HIV infection in the territory of Primorsky showed that women comprise 36,3% and men 63,7% of the population (ratio of women to men of 1:1,75). However, an increasing number of women over the last 6 years are presenting with newly diagnosed cases of HIV infection, and the percentage of women in the cumulative population has increased from 30% in 2004 to 38,3% in 2014. In general, the nature of opportunistic infections is comparable in both sexes. However, significant differences are observed in cases of *Candida* esophagitis, herpes infection, and cytomegalovirus infection. These diseases are more common in women in the form of gynecological

diseases from the ovaries, uterus, cervix, vagina, and labia and manifested by disorders of menstruation, inflammatory diseases of the pelvic, genital herpes infection; vaginal candidiasis; virus infection human papilloma lesion of the cervix (dysplasia, carcinoma). This is reflected in the inpatient care that women were more likely than men (80% versus 20%, respectively). Differences have also been observed in the incidence of other infections, such as skin disorders (rash, seborrhea, psoriasis, eczema, molluscum contagiosum, cellulite, tinea corporis and tinea), which are often more prevalent in women than in men. Among men who were examined by specialists, more often than women noted changes on the part of organs of vision (37,5% and 12,5%, respectively), nervous system (45.4% and 20%, respectively). We also found an increased incidence of urinary tract infections, fungal infections, and infections of the skin and nails in women relative to men, but a higher frequency of diseases of the peripheral nerves and muscles in men. Women experience changes in otorhinolaryngological organs more often than do men (36.4% versus 25%, respectively).

Conclusions

Monitoring of the clinical treatment of individuals with HIV can provide useful information for making management decisions that improve the quality and efficiency of medical care for HIV patients. Information obtained about progress in the clinical treatment of HIV-infected individuals and versatile monitoring of clinical examinations allows for the prompt coordination of the activities of specialists in medical facilities when working with HIV-infected patients.

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Chapter 13

**SPECTRUM PULMONARY LESIONS
AT HIV INFECTION**

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We conducted a study of clinical data on community-acquired pneumonia in immunocompromised patients with HIV infection. The data reveal the extent of the clinical course of the pneumonia. The data obtained reflect the severity of the clinical course and quite a wide range of opportunistic infections, caused illness.

Keywords: HIV, pneumonia, etiology, clinical features

Background

HIV infection is one of the most severe medical problems worldwide[1]. So as far as the progression of immunosuppression in patients with HIV infection is expanding the variety of lung diseases[2]. Pneumonia caused by different infectious agents plays a leading role in such diseases.

Objective

To study the spectrum of lung diseases in patients with HIV-associated immunodeficiency based on clinical, laboratory, and instrumental data.

Materials and Methods

Case records of 50 HIV-infected patients with lung diseases, hospitalized in the AIDS center of the city of Vladivostok in 2014, were analyzed.

Results of the study

Men prevailed (67%); the mean age of patients was 37 ± 7.8 years. Patients were diagnosed with stage 4B HIV infection (22% of cases; 11 patients), stage 4C infection (78% of cases; 39 patients). The average CD4 + T-lymphocyte count varied from 50 to 698 cells/ml. The preliminary

diagnosis for all patients upon admission was community-acquired pneumonia, mixed etiology, moderate severity. During subsequent examination, treatment, and observation, and according to additional laboratory and instrumental tests and assessment of clinical symptoms, the cause of pneumonia was mixed bacterial and fungal microflora with the prevalence in the bacterial spectrum of pathogens of *S. pneumoniae* (56% of cases; 28 patients), tuberculosis (30% of cases; 15 patients), and *Pneumocystis pneumonia* (10% of cases; 5 patients). Moreover, pulmonary tuberculosis and *Pneumocystis jirovecii* were more often detected in patients with CD4 + T-lymphocyte counts of <200 cells/ml (41,6% and 12,5%, respectively) than in patients with CD4 + T-lymphocyte counts of >200 cells/ml (19,2% and 7,7%, respectively). In addition, non-Hodgkin's lymphoma with metastasis to the lungs and pulmonary aspergillosis were diagnosed in patients with severe immunodeficiency.

Conclusions

Thus, when the progression of HIV disease in the spectrum of pulmonary lesions increases the incidence of tuberculosis and rare opportunistic diseases.

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SECTION 4

Functional Foods

Chapter 14

**INFLUENCE OF SE-ENRICHED LAMINARIA JAPONICA
ON EXPERIMENTAL RATS HEPATITIS**

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The sample of a brown alga *Laminaria japonica* powder with the selenium content meeting the recommended daily consumption dose has been received. Positive influence of a Se-enriched laminaria on the liver and blood serum biochemical parameters of laboratory rats against the experimental toxic hepatitis has been shown.

Keywords: selenium, selenium-enriched *Laminaria japonica*, experimental toxic hepatitis

Much attention has been paid to selenium in recent decades. Selenium is a micronutrient which deficiency in a human body is followed by the reproduction violation, by the heart muscle, bone and cartilaginous tissue damage. It plays an essential role in the cells antioxidant protection, cellular immunity maintenance, it is necessary for the thyroid and prostata glands normal functioning and for the spermatogenesis active course (Badmaev et.al., 1996; Francescato et.al., 2001; Moak M.A., Christensen M.J., 2001; Stone et.al., 1989; Vitoux et.al., 1996; Zust et.al., 1996). Selenium shortage aggravates diseases of respiratory organs (Coursin, Cihla, 1996). Selenium deficit was found in patients with malignant diseases of blood (Avanzini, 1995). Experimental deficiency of selenium results in the development of intestines cancer in rats (Jao et.al., 1996) and skin cancer in mice (Ohet et.al., 1995). In some cases positive correlation of selenium level in blood and frequencies of some types of oncological diseases in people was found. Seaweeds and products of their processing are a perspective source of organic selenium. The experiments were carried out to study the ability of macro seaweed

commercial species to accumulate selenium, as well as to obtain the biomass enriched with selenium.

The samples of 2-year old *Laminaria japonica* used in the experiments were selected from the marine cultures plantations of the Livadiya farm (Primorye Territory). The dynamics of the selenium accumulation by *L. japonica* thallomes in water with the element high concentration was investigated in the conditions corresponding with the optimum natural environment of seaweeds growth. Seaweeds thallomes were dried at the temperature of 40°C up to the constant weight, crushed in the laboratory homogenizer up to a powdery state.

Experimental hepatitis in white rats was caused by the oral introduction of 50% tetrachlormethane oil solution in the volume of 0,4 cm³/100g of an animal weight once a day during 14 days. After 14 days of introduction of four-chloride carbon the rats food was supplemented with crushed laminaria enriched with selenium during 21 days.

To assess pharmacotherapeutic efficiency of the laminaria powder two groups of experimental animals were used. The rats diet was supplemented with laminaria powder in the selenium doses of 10 mkg / 100g (group I) and 0.4 mkg / 100g (group II). The animals conditions were evaluated on the 14th and 36th days of the experiment by the biochemical indicators against the animals unaffected by CCl₄ (intact group) as well as to the sensitized animals, which were not treated by the laminaria preparation (control group).

Selenium concentration in algae increased proportionally to its content in the environment conditions (Table 1).

Table 1 – Selenium concentration in *L. japonica* thallome in seawater with different selenium contents ($M \pm m$, $N = 6$)

Time of exposition, days	0.01 mg/L	0.10 mg/L	0.50 mg/L	0.50 mg/L/day
0	1.34 ± 0.32	1.34 ± 0.32	1.34 ± 0.32	1.34 ± 0.32
3	1.47 ± 0.53	1.95 ± 0.47	3.64 ± 0.22	10,64 ± 1,8
6	1.59 ± 0.30	2.47 ± 0.26	5.18 ± 0.58	41,92 ± 7,1
10	2.35 ± 0.46	4.19 ± 0.36	9.83 ± 0.40	54,50 ± 9,3

Maximum selenium content in *Laminaria japonica* thallome was achieved on the 10-th day of exposition, it was equal to 54.5 µg/g. This value was about by as much as 40 times greater than that of the control samples, and it corresponded to the RDA for human consumption.

Therefore, algae biomass, the selenium content in 1 g of which, was equivalent to the recommended daily human consumption norms was obtained.

The selenium protective properties determine its preparations application under the action of various toxicants. In this regard, the dry selenium-enriched *L. japonica* powder effect on the pro- and antioxidant systems of the laboratory animals at experimental toxic hepatitis was investigated.

The tendency of reducing the selenium concentration in liver and blood of the control group rats against the intact group was found on the 14-th day of the experiment (Table 2). It might be due to the selenium-containing compounds active spending during the CCl₄ - initiated pathology progression. The selenium concentration in blood is an objective factor of the body's selenium status. This value shows the total contain of active selenium-contained enzymes, selenium-transporting proteins, and repository selenium (Tutelyanet.al.,2002). The localization of the excess selenium in the animal tissues is not clear but the selenium accumulation is supposed to be connected with glycoprotein SeIP - basic selenium-containing protein of mammals plasma (Vendeland et al., 1993). This protein can perform intracellular selenium transportation, as it is fast regenerated and consists of 9 – 12 selenium - cysteine remnants depending on the body type. It is also known that SeIP synthesis is becoming more active with selenium-containing additives to the selenium-deficit animals diet (Calvin et al., 1981).

Table 2 – Selenium concentration in liver (µg/g) and serum (µg/L) of rats under the influence of Se-enriched *Laminaria japonica* powder against experimental toxic (CCl₄) hepatitis (M ± m, N = 5)

Day of the experiment	Intact rats	Rats with experimental toxic hepatitis		
		control	group I	group II
liver homogenates				
14	0.29 ± 0.07	0.20 ± 0.05	-	-
36	0.22 ± 0.06	0.12 ± 0.04	0.40 ± 0.09	0.84 ± 0.16
blood serum				
14	75 ± 9	86 ± 11	-	-
36	68 ± 10	74 ± 8	92 ± 10	274 ± 24

Using selenium-enriched *L. japonica* in the daily ration resulted in the dose-dependent selenium accumulation in the rats liver and blood. On the 36-th day of the experiment the selenium concentration in the liver in

the group I animals increased by as much as 3 times, but this parameter in the blood serum was at the level of the control group animals. As for group II the selenium level in the serum and liver increased by as much as 7 and 3.7 times respectively.

The specific indicators of the lipid peroxidation process (LPO) development are known to be dieneconjugates concentration of unsaturated higher fatty acids (DK) – the products of the first stage of the oxidation process and malondialdehyde (MDA) concentration – the final product of bio-membrane oxidation. The dynamic of DK and MDA changes in the experiment with *Laminaria* is shown in table 3.

The results showed the significant change of DK and MDA generation. Strong liver damage was found in the control group rats. Higher selenium doses mixing in the diet (group II) resulted in the animals state normalization.

MDA definition is not always an adequate criterion of the lipid peroxygenation process development degree, due to the insufficient specificity of this reaction (Nikolayev, 1992). However, even if the peroxidation products are not registered but there are changes of the antioxidant system components, in particular, reduced glutathione, it can be stated that the free-radical oxidation processes are activated (Tutelyanet, al., 2002).

The reduced glutathione concentration in the rats liver homogenate was determined for this purpose (Table 3).

A two-fold increase of the reduced glutathione in the rats liver fed with selenium enriched *L. japonica* is the indication of the algae powder antioxidant properties.

Table 3 – Some biochemical parameters of rats liver and serum under the influence of Se-enriched *Laminaria japonica* powder against the experimental toxic (CCl₄) hepatitis on the 36-th day of the experiment (M ± m, N =5)

Parameter	Intact rats	Rats with experimental toxic hepatitis		
		control	group I	group II
Diene conjugates concentration, $\mu\text{mole/mg of protein}$	liver homogenate			
	2.86 ± 0.56	3.81* ± 0.28	3.78 ± 0.28	2.91* ± 0.27
Malondialdehyde concentration, $\mu\text{mole/mg of protein}$	liver homogenate			
	0.27 ± 0.03	0.48* ± 0.02	0.40 ± 0.04	0.30* ± 0.02

Reduced glutathione concentration, $\mu\text{mole/mg of protein}$	liver homogenate			
	4.58 ± 0.33	$3.25^* \pm 0.23$	5.13 ± 0.35	$6.26^* \pm 0.42$
Glutathione peroxidase activity, $\mu\text{mole GSH/mg protein/min}$	liver homogenate			
	4.78 ± 0.07	$3.15^* \pm 0.03$	5.13 ± 0.06	$6.26^* \pm 0.03$
	serum			
	1.39 ± 0.04	$1.22^* \pm 0.05$	1.53 ± 0.04	$1.46^* \pm 0.05$
Cholesterine concentration, mmole/mL	serum			
	3.00 ± 0.18	$3.88^* \pm 0.13$	2.93 ± 0.37	$2.75^* \pm 0.33$
α -tocopherol concentration, mg/g	liver homogenate			
	18.3 ± 3.7	$24.5^* \pm 4.9$	$5.7^* \pm 1.1$	$196.1^* \pm 19.2$

Varieties are statistically significant at $p < 0.05$

The glutathione peroxidase (GPX) activity, which shows the level of selenocysteine accumulation and its integration in the molecule structure, is the indicator of the body selenium status in common with the blood serum selenium content (Levander, Burk, 1998). After adding $0.4 \mu\text{g}$ of selenium per 100 g of the rats body weight to the daily diet of the sensitized animals the GPX activity in the liver homogenate increased by as much as 1.6 times and when the selenium dose was increased up to $10 \mu\text{g}/100 \text{ g}$ of the rats body weight the GPX activity in the liver homogenate increased by as much as 2 times. The analysis of the enzyme activity in the blood serum of both animal groups showed that this indicator increased by about as much as 1.3 times in both cases (Table 3). These results confirm the antioxidative effect of selenium enriched laminaria.

One of the important syndromes which can be found in the damaged hepatobiliary system is a cholestasis caused by the production abnormality and bile outflow. The reason of its development is the enzyme system, bile acids and cholesterine metabolism inactivation (Moak, Christensen, 2001). The experiment showed that the cholesterine concentration in the blood serum of the control group rats was up to 30 % higher than that in the intact rats (Table 3), which also confirms the liver toxic damage. The selenium enriched *L. japonica* introduction into the animal diet decreased the cholesterine level to the initial condition.

Vitamine E (α -tocopherol) is considered to be the main LPO regulator. The concentration of α -tocopherol was also found in the liver homogenate and blood serum (Table 3).

The decrease of the α -tocopherol level by as much as 4 times was found in the liver of rats receiving small dose of the selenium preparation. When selenium was increased in the diet by as much as 5 times, the vitamin E concentration in the animals liver increased by as much as 8 times.

Dramatic increase of the α -tocopherol concentration in the liver of the group II rats is consistent with the ideas of the synergism effect of selenium and vitamine E (Hoekstra, 1975; King, McCay, 1983; Ip, 1985).

So, the obtained results of the experiment showed the positive effect of selenenriched *L. japonica* powder as the therapeutic preparation in the process of the rat experimental toxic hepatitis. The selenium concentration level increase in the blood serum and the GPX activity increase in the experimented animals demonstrates good fixation of this product elements. So, such kind of algae can be used for obtaining selenenriched biomass in the bioactive additives and functional food production.

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Chapter 15

**DEVELOPMENT OF FUNCTIONAL BURDOCK
ROOT-BASED BEVERAGES**

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Abstract: Formulations for functional burdock-root-based beverages were developed. Milled burdock root was hydrolyzed with citric, acetic, or ascorbic acid to split its constituent inulin to form glucose, to reduce the amount of sugar in the beverages. The hydrolyzed-burdock-root-based beverages developed had an original taste and had few calories.

Keywords: functional drinks, burdock, burdock root, inulin, fructose, ginger juice, chicory, diabetes

Proper nutrition is an important factor in human health. An unbalanced diet results in metabolic disorders, diseases of the gastrointestinal tract, and disorders of the endocrine system. Poor nutrition can also accelerate the development of various pathological processes and cause their progression in the body.

As reported by Russian and foreign scientists, the pathologies and diseases of civilized countries are caused by the inadequate consumption by the population of vitamins, macro- and microelements, polyunsaturated fatty acids, dietary fiber, and essential amino acids rather than by the excessive consumption of animal fats.

Based on the scientific theory of balanced and adequate nutrition, different kinds of food can be considered dietetic, prophylactic, medical and prophylactic, therapeutic, healthy or optimal, or functional.

The concept of “functional” foods was first formulated in Japan in the early 1980s. “Functional” foods are products that contain natural and organic substances enriched with vitamins or microelements, which have certain useful properties (energetic, probiotic, etc.) [2]. Proper

nutrition that is adequate and safe is one of the key elements of a healthy lifestyle. Beverages are a large part of the food that people consume on a daily basis.

Beverages that can be assigned to the group of “healthy” drinks are considered in this paper. Healthy drinks are intended for mass consumption, and therefore they are the most popular functional beverages. They must be enriched with vitamins, minerals, unsaturated fatty acids, and dietary fiber, which contribute to the prevention of diseases of the cardiovascular system and gastrointestinal tract, including cancer.

Wild plants are known to be sources of functional ingredients, including dietary fiber, biologically active compounds, vitamins, and minerals. The natural habitats of these plants allow them to accumulate the highest levels of useful components. Burdock (genus *Arctium*) is one of these wild plants.

Eight species of burdock grow in Russia, and three types of them grow in the Primorye Territory: great burdock (*A. lappa*), smaller burdock (*A. minus*), and woolly burdock (*A. tomentosum*). The chemical composition of burdock is well studied. The plant roots contain 15.4% protein, 1.5% fat, 22.3% fiber, essential oils, and palmitic and stearic acids. The roots of the plant also contain 45% inulin polysaccharide, which restores the function of the human digestive system. Inulin, when subjected to acid hydrolysis, is a source of fructose, which is extremely important in the diet of people with diabetes mellitus.

Great burdock (*A. lappa*) root grown in the Primorye Territory, collected in July–August when it is most succulent, was used for the experiments. To prepare the beverages, dried and roasted burdock root was ground to a fine homogeneous powder. To prepare the beverage, 8 g of burdock root powder was boiled in 200 ml of water.

Because the burdock root is rich in inulin polysaccharide, which forms fructose when split, it can be used to replace (wholly or partially) the sugar usually added to beverages. The inulin in the burdock root was acid hydrolyzed for this purpose. The dried roots were shredded before hydrolysis. The amount of inulin in the burdock root infusion was determined with a previously reported method [3]. The inulin was hydrolyzed with 6% citric, acetic, or ascorbic acid at a temperature of 75 °C for 60 min. To qualitatively assess the hydrolysis of inulin, we used the naphthorezorcic mucic acid test, which measures the reaction product, fructose [4]. The fructose content was determined as the intensity of the

solution color on a spectrophotometer (UNICO-1201) at a wavelength of 800 nm. The results are shown in Figure 1.

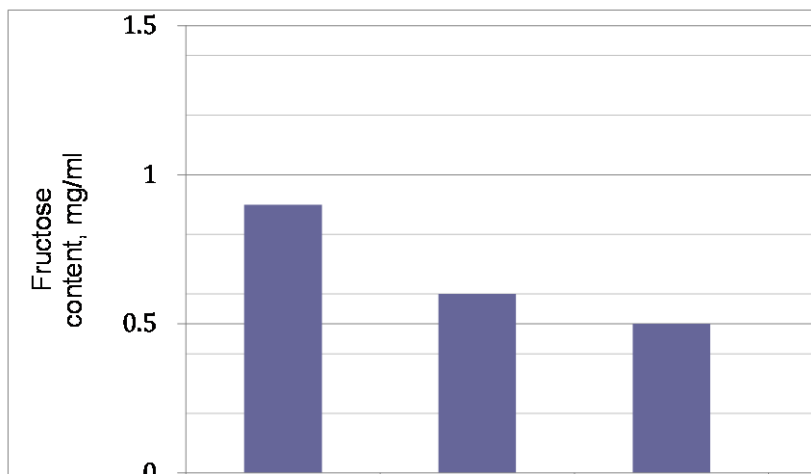


Figure 1. Fructose content in the burdock-root-based infusions.

The greatest amount of fructose (1.4 mg/ml) was present in the sample treated with ascorbic acid, which was considerably higher than that in the samples treated with acetic or citric acid. The inulin contents in these samples were 0.6 and 0.5 mg/ml, respectively. The acid strength clearly influenced the degree of inulin hydrolysis. Ascorbic acid showed the greatest oxidation-reduction potential among this series of acids, resulting in more complete inulin hydrolysis.

To increase the degree of inulin hydrolysis and the fructose content, the beverage was supplemented with ginger root, which contains up to 12 mg/100 g ascorbic acid. Ginger root also contains many valuable compounds, particularly asparagine, choline, linoleic, oleic, and caprylic acids, essential oils, vitamins B1, B2, and B3, and a saturated mineral complex (silicon, aluminum, zinc, sodium, phosphorus, iron, manganese, potassium, magnesium, and others).

To prepare a burdock-root-based beverage, 10% (by product volume) ginger was added as a juice, to make the taste better. A second drink, containing chicory root as well as ginger juice, was prepared to enrich the infusion with inulin and to add a racy coffee flavor. Chicory is a source of inulin, with an inulin content of 49%–60%. Based on organoleptic indicators, the burdock-root-based drink was supplemented

with 10% (by product weight) shredded chicory root. The introduction of chicory root into the beverage increased its biological value and functional focus, because chicory root contains flavonoids, catechol tannins, glycosides, carbohydrates, unsaturated sterols, coumarin, sesquiterpene lactones, and triterpenoids [1].

The fructose contents of the prepared beverages were determined with a previously described method, and the results are shown in Figure 2.

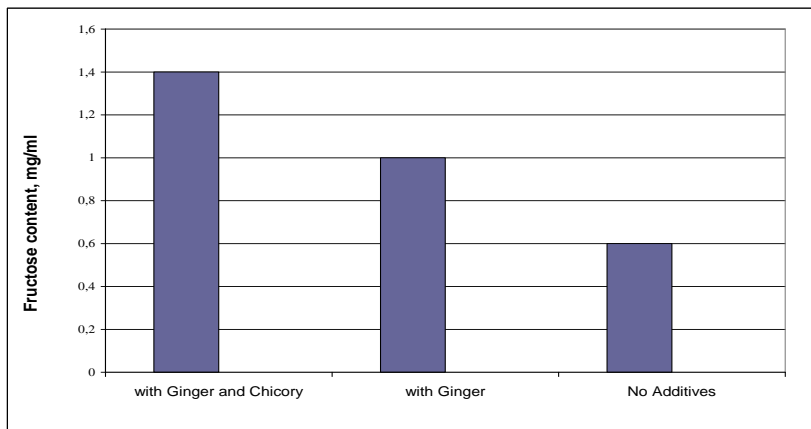


Figure 2. Fructose contents of the burdock-root-based beverages.

The infusion supplemented with ginger juice and chicory root contained the largest amount of fructose (1.4 mg/ml). The infusion supplemented with ginger juice contained somewhat less fructose (1 mg/ml). The fructose content of the burdock-root-based beverage with no additives was 0.6 mg/ml, which was 2.5-fold less than that of the beverage containing ginger juice and chicory root and 1.5-fold less than that of the beverage containing ginger juice.

We deduced from these experiments that while preparing functional burdock-root-based beverages, it is necessary to supplement them with organic acids, such as ascorbic acid, because their contents of the acids and enzymes that catalyze hydrolysis are insufficient for the complete hydrolysis of inulin.

The burdock-root-based beverages prepared had high organoleptic properties. The optimal chemical composition was created in the beverages, giving them a wide range of flavor properties. The burdock-root-based beverage supplemented with ginger juice and chicory

root was the most original according to its organoleptic indicators. The original taste and flavor of the drink were attributable to the successful combination of the grassy–nutty flavor of roasted burdock root, the pungent taste of ginger juice, and the coffee aroma and taste of chicory. As this study shows, the addition of ginger juice to the drink formulation reduced its sugar content by as much as 5%, because it increased the degree of inulin hydrolysis.

The hydrolyzed burdock-root-based beverage developed here has a feature of low calory drink (51.3 kcal/200mL) and contains the inulin hydrolysis product, fructose. This beverage can be recommended for dietetic nutrition and for people suffering diabetes mellitus. This multicomponent burdock-root-based beverage, supplemented with ginger juice and chicory root, can be offered as an enriched functional beverage and a source of valuable biologically active substances and soluble dietary fiber.

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Chapter 16

**ANTIOXIDANT ACTIVITIES OF MANCHURIAN
WALNUT-PERICARP-BASED EXTRACTS**

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Abstract:

The feasibility of using Manchurian walnut pericarp extract in therapeutic and prophylactic products was investigated. The antioxidant activities of extracts were examined according to the maturity of the Manchurian walnut. The fresh Manchurian walnut pericarp has the highest antioxidant activity in the milk maturity stage.

Keywords: Manchurian walnut, Manchurian walnut pericarp, milk maturity stage, harvest maturity stage, antioxidant activity.

The health status of the world population currently displays a negative trend. Both Russian and foreign scientists have attributed the pathologies and diseases of civilized countries to socioeconomic and environmental degradation and a decline in nutritional quality. The lack of nutrients in the diets of modern humans contributes to increases in diabetes mellitus, atherosclerosis, coronary heart disease, gastrointestinal tract diseases, and a variety of malignancies.

Disease prevention is the primary objective of current medicine. Healthy nutrition is important for disease prevention, and should include the complete complement of vitamins, micro- and macroelements, and substances that prevent or reduce the negative impact of radioactive elements and toxic compounds that enter the human body.

Wild plants are known sources of biologically active compounds, vitamins, and minerals. The natural habitats of these plants allow them to maximally accumulate useful constituents. One of these wild plants is the

Manchurian walnut (*Juglans manshurica* Maxim), which grows in the far east of Russia, particularly in the Primorye Territory [2].

The chemical composition of the Manchurian walnut is well studied, and its pericarp is most biochemically valuable. It contains quinones (juglone), 0.03% alkaloids, 12%–14% tannin and coloring agents, 2.6% dietary fiber, 18.4% pectin, up to 12% mineral substances, 0.8% vitamin C, and flavonoids (quercetin and isoquercitrin) [1]. The medicinal properties of the Manchurian walnut pericarp are attributed to its rich chemical composition, and its antioxidant, antibacterial, antiparasitic, and antitumor properties. Therefore, to study the antioxidant activity (AOA) of the Manchurian walnut pericarp according to its ripeness stage and storage conditions is of the utmost interest [3].

The Manchurian walnut pericarps in the milk maturity stage (harvested in June) and the harvest maturity stage (harvested in October) were examined in the study. Fruiting is seasonal in the Manchurian walnut, but the raw material for the extracts is required all year round, so we investigated its optimal mode of storage. Three ways to store Manchurian walnut pericarp have been suggested: drying at 23 °C for a month, drying at 105 °C for 6 h, and freezing at –18 °C. The extracts used to determine its AOA were prepared by extracting fresh Manchurian walnut pericarp or Manchurian walnut pericarp treated with water in a ratio of 1:5 at 60 °C for 30 min.

The AOA of the Manchurian walnut pericarp extracts was investigated with the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method. The method is based on DPPH recovery promoted by antioxidant [4]. Eight samples of Manchurian walnut pericarp extract were examined according to the stage of fruit ripening and the storage conditions used; the results are shown in Table 1.

Table 1. Antioxidant activities of Manchurian walnut-pericarp-based extracts.

Maturity Stage	Storage Method	Ascorbic acid (AOA) mg/ml
Milk	Fresh	1251.67
	Dried at 23 °C	1141.18
	Dried at 105 °C	463.34
	Frozen at –18 °C	1102.97
Harvest	Fresh	543.54
	Dried at 23 °C	389.74
	Dried at 105 °C	149.36
	Frozen at –18 °C	286.52

Table 1 shows that the fresh Manchurian walnut pericarp in the milk maturity stage had the highest AOA (1251.67 mg/ml of ascorbic acid). Minor losses of AOA occurred during the process of drying at 23 °C and during freezing at –18 °C. The AOA values were 1141.18 and 1102.97 mg/ml of ascorbic acid with these storage methods, respectively. Significantly lower AOA values were observed during product drying at 105 °C, equivalent to 463.34 mg/ml of ascorbic acid. AOA is probably lost from the raw material with the degradation of biologically active compounds at high processing temperatures.

The AOA of the Manchurian walnut pericarp was considerably lower in the harvest maturity stage than in the milk maturity stage. Analysis of the data showed that the Manchurian walnut pericarp extracts had quite high AOA. The Manchurian walnut-pericarp-based extracts can be used in the food industry to develop a wide range of product formulations for therapeutic and prophylactic purposes.

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SECTION 5

Therapy

Chapter 17

**A REVIEW ON THE WHOLE BRAIN IRRADIATION
WITH PRESERVATION OF THE HIPPOCAMPUS**

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Rationale for hippocampal sparing

The hippocampus contains primordial neural stem cells and plays several important roles in the brain, including spatial navigation and the consolidation of new information to the fixed memory. Injury to the hippocampus due to stress, aging, toxins, chemotherapy, and radiotherapy can cause amnesia, cognitive disorder, disorientation, and a deterioration of brain function. Accordingly, sparing of the hippocampus has been a focus of recent technological advances in radiotherapy.

Whole-brain irradiation (WBI)

WBI is indicated for various clinical scenarios, which include prophylaxis for subsequent brain metastasis after complete remission of leukemia and small cell lung cancer, in the treatment of central nervous system lymphoma, and for multiple brain metastases. However, it is problematic that WBI is associated with the sequela of significant cognitive deterioration. WBI is generally performed with 30 Gy/3 Gy \times 10 fractions for two weeks. In the results of the RTOG 0933 phase I trial, Gondi et al. 2014 reported there was a mean relative decline of 7.0% after WBI with hippocampal sparing between baseline and 4 months for the Verbal Learning Test–Revised Delayed Recall Score, while a historical control without hippocampal sparing demonstrated a mean relative decline of 30% ($P < .001$) following WBI. They concluded that conformal avoidance of the hippocampus during WBI is associated with preservation of memory and quality of life, as compared with historical series.

Stereotactic brain irradiation (SBI)

Individual to widespread brain metastases can be treated in single or multiple sessions using a stereotactic beam convergence technique such as Gamma Knife or Cyberknife, with a single dose of 20 Gy or fractioned doses of 50 Gy/5 Gy \times 10 fractions, usually without whole brain coverage. The effectiveness of SBI is well established as a superior alternative to conventional WBI of 30 Gy/3 Gy \times 10 fractions to 40 Gy/2 Gy \times 20 fractions when the number of the gross metastatic lesions was small. This technique efficiently targets the gross tumors but has the drawback that it does not cover residual tumor. However, because of the risk of cumulative brain damage, additional WBI is not recommended if SBI has already been performed.

Concomitant WBI and SBI

Technically, tomotherapy enables concomitant WBI and SBI. We developed the following prescription for simultaneous delivery of SBI and WBI over two weeks: 50 Gy/5 Gy \times 10 fractions to the gross tumor volume(s), and 30 Gy/3 Gy \times 10 fractions to the rest of the brain as prophylactic therapy, respectively. Because there is no established clinical evidence regarding the safety and efficacy of this strategy, we have used this protocol at our institute only for selected groups of patients those with high risk of dissemination and mental deterioration. We are currently accumulating clinical cases with the aim of evaluating the availability and reliability of concomitant WBI and SBI, and presenting our clinical findings.

Reference

Gondi V et al. Preservation of Memory with Conformal Avoidance of the Hippocampal Neural Stem-cell Compartment during Whole-brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial. J Clin Oncol. 2014 Oct 27.
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