NEW MECHANISM OF THE WATSON-CRICK MODEL OF GENETIC INFORMATION TRANSMISSION BY EXAMPLE OF NON-CYTOKINE REGULATION OF HEMOPOIESIS

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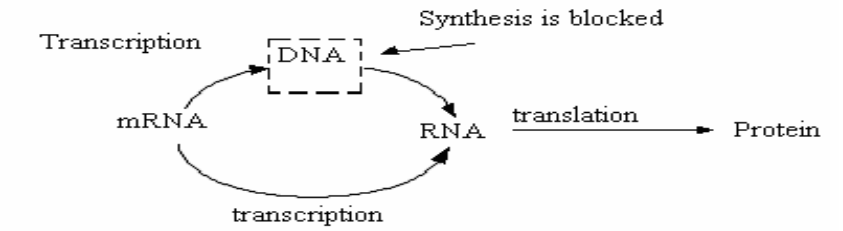
Our experiment proves conception, that interference of radiation frequency of wave energy hγ≈10^{13} Hz of ATP synthesis in plasmatic part of respiratory chain and resonance absorption of this energy frequencies by cellular genetic elements is physical nature of initiating signals to cell growth and cell proliferation through IAK-STAT-Kinase. As a result, it leads to smoothing frequencies of many conformational enzyme-substrate waves, and transmission of molecular signal from plasma membrane inside the nucleus according to the law of Determination L with energy of activation barrier Eact ≈ 0. It is shown, that influence of N-substituted 3-oxipyredine salts on normal and tumor cells results in considerable activation of RNA-polymerases with corresponding amplified duplication of normal RNA-transcripts and reduplication of newly created genetic information as a result of post-transcripts splicing into RNA-dependant DNA-polymerases. Therapeutic effects of the experimental compounds could substitute in clinic rHu G-CSF, rHu EPO, rHu TPO and other known remedies for treatment of anemia and thrombocytopenia of different genesis.

Realization of genetic information contained within the structural model of duplex DNA by J. Watson and F. Crick (1953) through transcription and translation is regarded as a universal code for all living organisms [1, 2]. Hereditary information is transmitted from DNA-template to protein synthesis in the following direction:

$$\text{DNA} \xrightarrow{\text{transcription}} \text{RNA} \xrightarrow{\text{translation}} \text{Protein}$$

However, we have presented experimental evidences in works [3-8], which overturn this common theory of molecular genetics. In particular, when DNA synthesis is almost completely inhibited as a result of the influence of N-substituted 3-oxipyredine salts on tumor cells of human ovarian carcinoma (CaOγ) at the same time RNA synthesis is stimulated by 214% compared with control values. At subcellular level (mitochondrion), cellular level (yeast, microorganisms, malignant cells) and organism levels (100000 drosophilas, 1200 non-pedigree rats and Vister rats, 10000 chickens, 30 calves, 52 young pigs, 107 cows with hemoblastosis and 36 monkeys) we showed, that the experimental salts cause epigenetic (non-genetic) selective stimulation of normal metabolic and physiological processes at higher animals [9].

The obtained experimental results could only be explained from position, that mRNA is a template of protein synthesis at higher animals in direction of selective distribution of normal copies of RNA-transcripts from one generation of animals to another during embryogenesis:



In 2005 epigenetic inheritance of mutant trait was proved for higher plants [10], and in 2006 – for higher animals [11]. Results provided in the latest works sparked discussions among specialists. In particular, Paul Soloway from the Cornell University marked in the covering letter to work by Minoo Rassoulzadegan and co-authors [11], that this research challenges modern ideas about hereditary.

But, to our opinion, there's no experimental ground not to regard DNA as a common carrier of hereditary information. Inheritance of mutant gene Kit at animal generation with normal genotype Kit+/+ on condition of different genetic variations of crossing [11] don't prove, that genetics laws are not working. They show that under influence of new experimental data new aspects of half-conservative mechanism of DNA reduplication are being revealed.

This report is concerned with experimental basing of a new mechanism of genetic information transmission in the Watson-Crick reduplication model on example of non-cytokine regulation of hemopoiesis of normal and tumor cells at higher animals and men by N-substituted 3-oxipyridine salts.

Activation of cell genome by resonance absorption of energy frequencies radiated by plasmatic ATP

Cells as a main structural functional unit of all living organisms normally adequately changes in response to external and internal signals towards activation of growth factors and conduction of proliferative stimulus into the cell nucleus [12].

Signal molecules include polypeptide hormones, growth factors, mitogenes, cytokines and some other molecular structures. Interaction of these molecules with specific receptors on cell membrane is an extremely difficult and to a large extent a poorly studied process.

To date, the number of basic interleukins (IL) has reached 23. Cytokines also include interferons, factors of tumor necrosis, growth factors, chemotoxic factors and others.

Effect of such big number of cytokines in regulation of hematogenesis and immunogenesis is mediated by specific receptors on cellular plasma membrane, for example, for family IL-6 – it's gp 130 [13]. Intermolecular reception and signal transduction from membrane to cell cytoplasm causes dimerization of gp 130. In the framework of molecular ideas it is a starting mechanism for activation of transducer chain, associated by attraction of receptor and non-receptor «family» of IAK-kinases.

The main purpose of A-Iak (Iak 1; Iak 2; Iak 3 and Tyk 2), Src-family (Blk; Fgr; Fyn; Lck; Hck; Lyn), C.Fps/Fes-family (c-fes type), D.Tec/Btk-family, E.Syk/ZAP70-family, VRK3, cAbl and a great number of other intracellular tyrosine kinases is phosphorylation and dephosphorylation of tyrosine bases of cytokine receptors' signal chain aimed at creation of specific areas for attaching SH2 – domains [13, 14]. It should be mentioned, that today only KINEOS antibody microarray service provides ultra sensitive analysis of about 600 signal-transducing proteins in phosphorylised condition.

Tyrosine bases of intracellular receptor, activated by phosphorylation, attract 7 inactive forms of Stats (signal transductors and activators of transcriptions), containing SH2 – domains. Tyrosine kinases activate Stats be means of phosphorylation, causing their dimerization, then they move away from the receptor and penetrate into cell nucleus, causing activation of specific DNA elements (fig.1).

So, this simple scheme of cytokine interaction with cells shows, that cytokine effects on cell come as a result of multiversion interactions, and conduction of cytokine signals to genetic elements is a very difficult and multi-step process.

Simple calculations show, that even having minimum 3-variant attempt and only 50 negative and positive regulators of signal transduction of cytokine stimuli inside the cell and ability of this cell to express specific properties at genetic level at a speed of $10^{10}s^{-1}$, that would require 3^{50} or 10^{50lg3} x 10^{-10}s 0 about 10^{7} years!

So, our calculations prove, that classic interpretation in the framework of molecular theories, for example, homodimer gp130 = gp130, as it were starting mechanism in initiation of signal from cytoplasmatic part of

gp130 to cell nucleus through JAK-STAT-KINASE [13] – is just nonsense.

To understand the nature of transcriptional genes activation by signal molecules we studied how synthesized salts [4, 6] of N-phenyl-3-oxipyridine (RL-175), N-hydroxyphenyl-3-oxipyridine (RL-S) and N-tolyl-3- oxipyridine (RL-3) influence on succinate oxidation rate in mitochondria of rat liver. It was shown, that under the influence of the experimental salts succinate is oxidized 60-80% stronger than in control: $1{,}14x10^{-6}$ s^{-1} compared with $0{,}67x10^{-6}$ s^{-1} in control, that corresponds with the same size acceleration of ADP phosphorylation into ATP. In skeletal and cardiac muscles of test rats, fed by experimental compounds, synthesis of ATP in vivo also increases by 2 and more times.

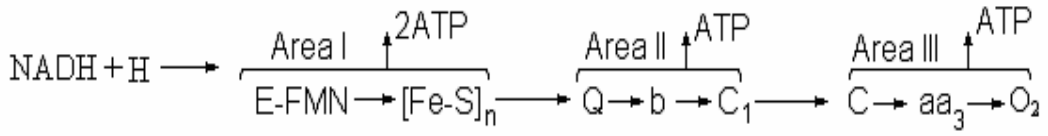
Authentic free energy (ΔG) of ATP synthesis in the above mentioned muscle cells when concentration of ATP, ADP and Pi are correspondingly 40; 0,93 and 8,05 мМ, pH value - 7,0 and provided 25^0C, equals as follows:

$\Delta G = \Delta G^{01} + 2{,}303\ RT\lg [ADP][Pi]/[ATP] = -51{,}9$ kJ/mole.

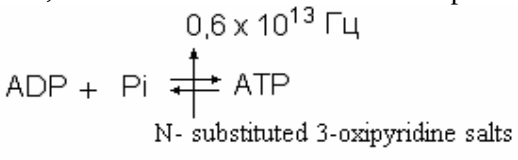
Where ΔG^{01} – standard free energy; R – gas constant; T - absolute temperature and Pi – phosphoric acid.

In standard thermodynamic conditions from -51,9 kJ/mole 30,5 kJ/mole are required for synthesis of one molecule ATP from ADP and Pi. The residual of -21,4 kJ/mole is standard energy (ΔG^{01}) of radiation in pool of multi-enzymatic complex of respiratory chain, which equals $Keq = 10^{-21{,}4\ /\ 5{,}7} = 5{,}62x10^3$ Hz.

Apparently, under the influence of N-substituted 3-oxipyridine salts 4 ATP molecules are synthesized in 3 key parts of respiratory chain. Normally there are 3 molecules [15].



Taking this into account, frequency of radiant energy during synthesis of 4 ATP molecules in three parts of respiratory chain is $0{,}56x10^{13}$ Hz and this value is comparable



with the frequency of resonance energy absorption by mitochondria of human hepatic cells ($3{,}18x10^{13}$ Hz) [16, 17].

It should be mentioned, that standard energy (ΔG^{01}) of electron flow from NADH to O_2 in the above mentioned respiratory chain equals [15, 18]

$$NADH + \tfrac{1}{2} O_2 + H^+ \rightleftharpoons H_2O + NAD^+$$

$\Delta G^{01} = -220{,}08$ kJ/mole.

122 kJ/moles are used for synthesis of 4 ATP molecules. Then from Planck equation $E=h\gamma$ of proportionality between absorbed and radiated energy at the same frequency in single act we can conclude the following: about 77,0 kJ/mole ($3{,}18x10^{13}$ Hz) from the remaining 91,5 kJ/mole fall at energy radiated by mitochondria of human hepatic cell, and the rest energy – heat dispersion. Radiation frequency calculated for mitochondria $0{,}6x10^{13}$ Hz - $3{,}18x10^{13}$ Hz is also comparable with frequencies of resonance energy absorbed by nuclear cell structures [16, 17]: with body cell of mammal ($2{,}39x10^{12}$ Hz), nucleus of body cell of mammal ($9{,}55x10^{12}$ Гц), human cell genome ($2{,}5x10^{13}$ Hz), chromosomal interphase ($7{,}5x10^{11}$ Hz) and metaphase ($1{,}5x10^{13}$ Hz), with genome subunits, which code protein with molecular weight of 50 thousand dalton ($< 9{,}7x10^{14}$ Hz) and other genetic elements.

For reference let us note that molecular weight of the known hemopoietins varies within the limits of 15-50 kDa (glycoprotein-IL-6 has 25 kDa) [19]. The level of molecular weights G-CSF, EPO and TPO is considerably smaller than 50 kDa [20].

So, from Planck equation $E=h\gamma$, which says that amount of radiated and absorbed energy in a single act of system is proportionate to frequency (γ), we can conclude, that physical nature of initiation of signal from cytoplasma to nuclear cell subelements lies in interference of frequencies radiated by plasmatic ATP and resonance absorption of this energy frequencies, for example, by genes of eukaryotic RNA-polymerases.

Interaction of equal frequencies of energy radiation and absorption energy leads to smoothing of quantum frequencies of conformational enzyme-substrate waves which results in activation or inhibition of molecular mechanisms of cell growth induction, amplification and transduction of this signal stimulus from plasma membrane to myelo-proliferative genes and vice versa, with energy of activation barrier $\Delta Eact \approx 0$, according to the law of Determination, during chemical transformations (fig.1) .

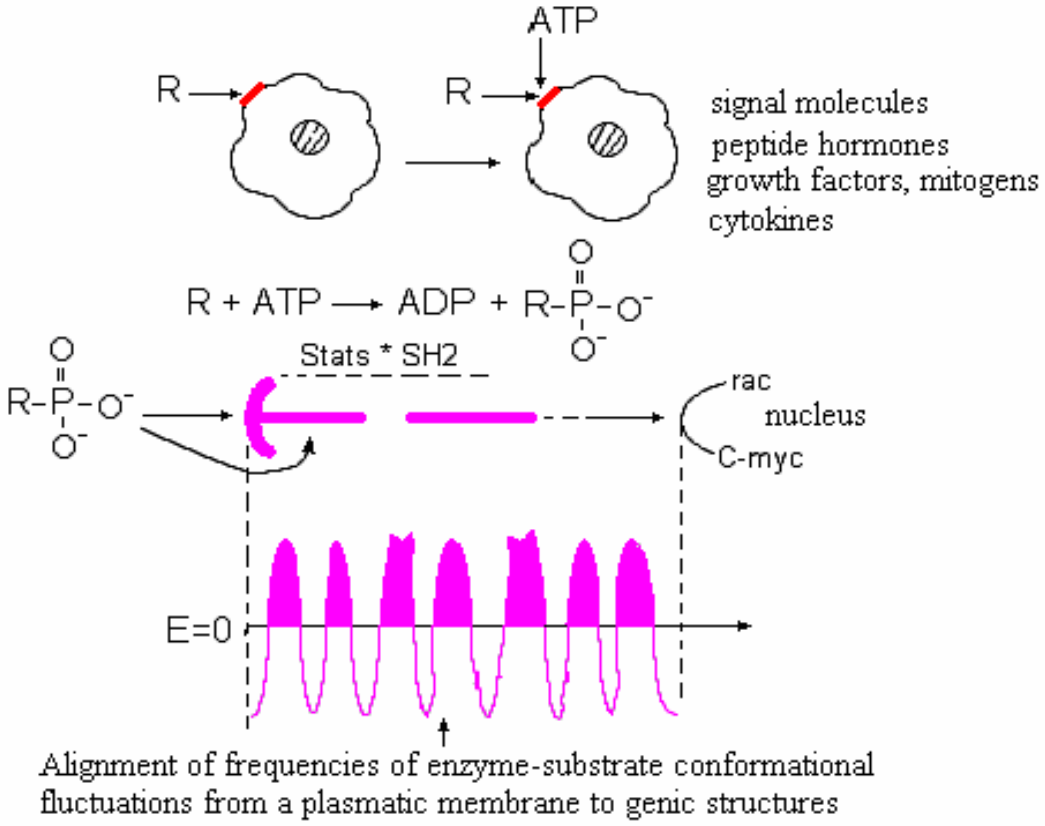


Fig.1. Scheme of intracellular conformational oscillatory–resonant signal transmission to transcriptional genes according to Law of Determination (L) [21]. Difference of free energy (E) between closed, spontaneously reacting initial and final systems $E = \Delta H + RT$ (where ΔH – enthalpy; R – gas constant; T – absolute temperature) – is an energy of activation barrier. Expression E is associated with the principle of uncertain coordinate and impulse (speed) of reacting particles in a well-konwn Geizenberg ratio, from which it follows, that not every collision leads to reaction product. For example, each active enzyme-substract collision accounts for 200 encounters [12]. In chemical transformations where $E \approx 0$ each encounter of particles is effective. These processes run according to the principle of Determination [21] unlike reactions where $E \gg 0$ and reacting particles need to acquire this energy in order to enter a chemical reaction during collision.

A number of authors have to some extent similar ideas as in our research in questions of synchronization of waves of many endogenous oscillators depending on external exogenous or endogenous factors [13, 16, 17].

Non-cytokine regulation of normal and tumor hemopoietic cells (G-CSF, EPO and TPO)

Cytokines G-CSF (Granulocyte colony-stimulating), EPO (Erythropoietin) and TPO (Thrombopoietin) don't have receptor tyrosine-kinas activity but have common chains in intracellular part of receptors [13, 14].

Extracellular receptor part of these chains is responsible for specific binding, and intracellular – for formation and transmission of cytokine signals to transcriptional genes. In response to influence of cytokines G-CSF, EPO and TPO on extracellular hemopoietic specific receptors of animal or human cell in aerobic conditions ATP is synthesized from ADP and Pi (fig.1) unlike its zero concentration in tumor cells [22].

Following these classic molecular theories of hemopoiesis regulation, we should have expected extremely low sensitivity of normal and tumor hemopoietic cells to the studied N-substituted 3-oxipyridine salts. This conclusion was based on the following: firstly, in experiment we showed [3], that N-hydroxyphenyl-3-oxipyridine almost completely inhibits activation of DNA in tumor cells of human ovarian carcinoma (fig. 2a, b) and secondly, N-substituted 3-oxipyridine salts do not inhibit tyrosine kinases, on the contrary, they considerably induce activation of receptor and non-receptor tyrosine kinases for growth factors of cells.

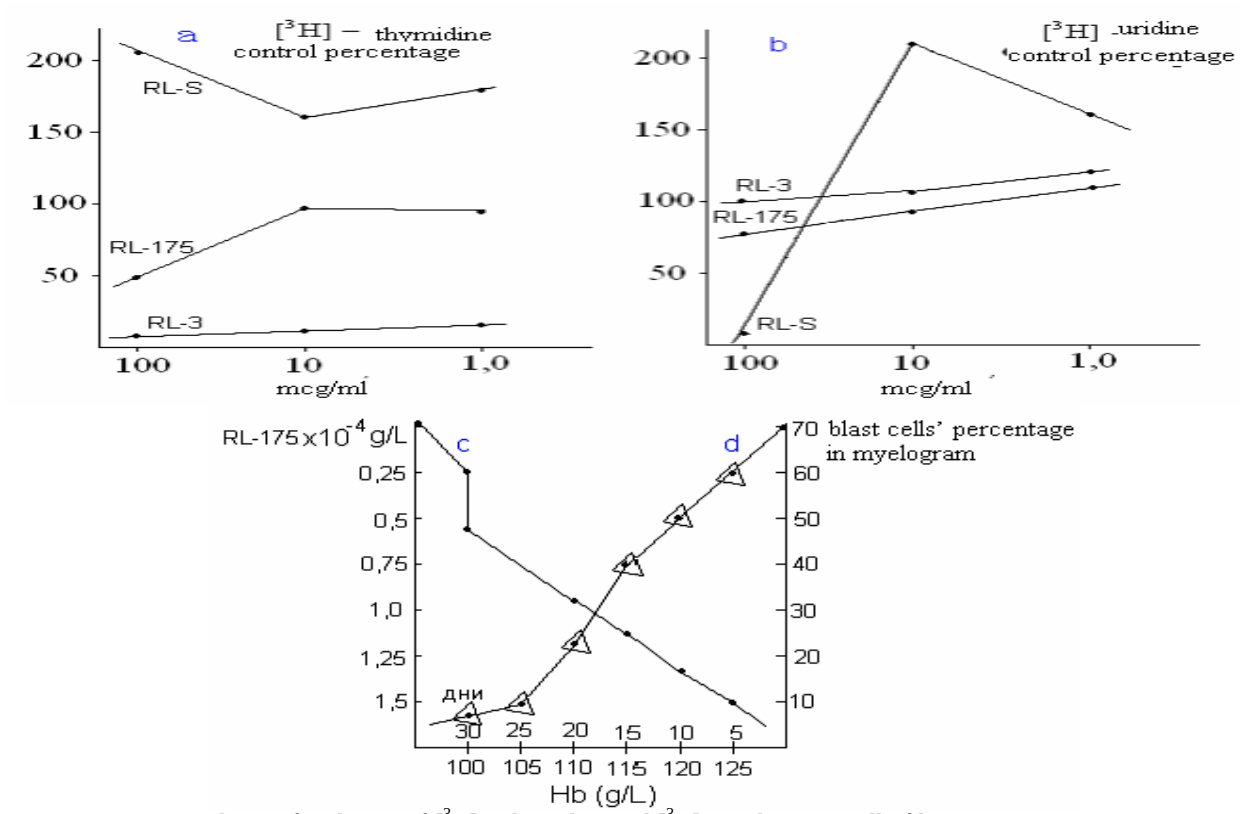


Fig. 2. Dependance of inclusion of [^{3}H] – thymidine and [^{3}H] - uridine in a cell of human ovarian carcinoma on concentration of preparations RL (a, b). Hb concentration icreases at 5 patients with ALL with chronic renal failure (c) and blast cells content in myelogramme reduces depending on the dose of RL-175. Diagnosis of these patients was classified in Russia's leading hematologic centres. All research on marrow cells, diagnostic punction before and after treatment by preparation RL-175, were conducted in the same scientific centres.

Due to this reason the experimental salts should have activated mechanisms of intracellular transmission, first of all, of tumorigenic signal stimulus to transcriptional genes [13, 22].

Results

The experimental compounds considerably induce non-cytokine growth regulation, differentiation and correction of normal and tumor hemopoietic cells (table 1-3, fig.2 c, d). We revealed how hemoglobin (Hb), erythrocytes (Ery) and leukocytes (Leuk) production in peripheral blood of animals depends on the dose of N- hydroxyphenyl-3-oxipyridine salt (RL-S). Optimal doses are: for female rats – 3-time total dose 2,4 $x10^{-5}$ g/L or for hemoblastosis cows – 15,9 $x10^{-5}$ g/L.

Table 1 Content change of haemoglobin (Hb), erythrocytes (Ery) and leukocytes (Leuk) in peripheral blood of animals depending on injection of different doses of RL-S ($p< 0,05$)*

Animal, physiological condition	Dose RL-S, g/L per heads $x10^{-5}$	Number of injections	Total dose g/L $x10^{-5}$	Hb /L	Ery $x10^{12}$ /L	Leuk $x10^{9}$ /L	Increase rate	
							Hb	Ery
Healthy rats (n=20):								
Control (n=10)	-	-	-	104±6,0	3,16±0,2	10,0±0,1	0,0	0,0
Test (n=10)	0,8	3	2,4	174±1,0	7,5±0,5	6,0±0,2	67,3	137,4
Healthy cows (n=50):								
Control (n=10)	-	-	-	98±6,0	6,4±0,5	6,9±0,5	0,0	0,0
Test (in each series n=10)	2,8	3	8,4	114±10,0	4,0±0,4	6,9±0,4		
	2,8	6	16,8	126±9,0	9,6±1,5	9,1±1,3		
	5,3	3	15,9	129±7,0	9,8±1,0	6,6±1,8	31,6	53,1
	5,3	6	31,8	89±16,0	7,5±1,8	10,0±1,3		
Cows with brucellosis (n=16):								
Control (n=6)	-	-	-	102±9,4	6,8±0,6	7,4±1,5	0,0	0,0
Test (n=10)	5,3	3	15,9	156±10,2	9,8±0,6	8,3±1,3	53,0	44,0
Cows with hematoblastosis:								
Control (n=10)	-	-	-	98±6,6	6,9±0,5	21,0±3,1	0,0	0,0
Test (n=10)	5,3	3	15,9	142±8,0	10,2±1,0	6,7±0,8	45,0	48,0

*Preparation was injected to animals intravenously during 7 days.

Hb and Ery content at healthy test cows increases from initial values by 30 and 53 % respectively, at rats - 67% and 140% (table 1); at hemoblastosis animals – 45,0 and 48% respectively. The effect of N-hydroxyphenyl-3-oxipyridine on Hb, Ery, Leyk values and other blood elements practically remains during 180 days after tests (observation time).

The same values for cows with brucellosis have increased: Hb - by 53% and Ery - 44%. Serum diagnostics revealed that after the course of treatment agglutination titer of antibody content in 1 ml of blood serum of sick animals shifted from 200-400 IU/L (International Units Liter) to zero (there was no agglutination in all serum doses).

Fig. 2c and 2d show average results of anemia correction in clinic during tests of N-phenyl-3-oxipyridine salt on 5 patients with acute lymphoblastic leukemia (ALL) c blast crisis. Patients with chronic kidney disease did not remit after traditional course of therapy using human recombinant rHu-EPO. At the same time after the course of treatment using

the experimental preparation in total dose 1,5 x10^{-4} g/L the same patients (ALL) had stable correction of anemia to norm and reduced content of blast cells in myelogram from 70% to 3,0%.

Tables 2 and 3 show results of clinical hematological research into effect of preparation N-phenyl-3-oxipyridine (RL-175) on 15 patients aged from 6 to 65 (average age is 26), with thrombocytopenia of different genesis (central and peripheral). Before approbation by the studied preparation all patients underwent complete courses of therapy in Russia's leading Hematological Centers in 1990-2000.

At the 3rd and further stages of relapse effect of traditional treatment at all patients reduced almost till zero level (positive anti-tumor effect). Patients did not remit, they had an unfavorable prognosis for the disease.

Depending on the clinical peculiarities of disease course all 15 patients were divided into 3 groups. The 1st group included a 16-year old boy diagnosed with chronic immune thrombocytopenic purpura (ITP).

The 2nd group included 5 female patients with hereditary idiopathic thrombocytopenic purpura, and the 3rd – 9 female patients with thrombocytopenia, caused by aplasia of myeloid stem cells.

Criteria for choosing these 20 patients for approbation by N-phenyl-3- oxipyridine (RL-175) were the following: voluntary agreement of patient, strict verification of diagnosis, evaluation of patient's condition, very low results of traditional therapy and others, according to ethic norms and requirements, and also standards, stated in Helsinki Declaration of 1975 (resisted in 1983).

Patient G.V. - a 16-year-old boy - applied in December, 1991 to the North-Ossetian center of medical-biologic problems (Vladikavkaz, Russia) diagnosed with immune thrombocytopenic purpura (ITP). Since June, 1991 he has undergone treatment in several Russian clinics, but despite higher dose of prednisone in combination with Immune Gammaglobuline (IVIG), as well as transfusion of thrombocytes concentration he never remitted.

Acute condition was accompanied by nose and gingival bleeding, hemorrhagic skin rash and weakness.

On 01.21.1992 patient G.V. began to take preparation N-phenyl-3-oxipyridine per os. By 02.16.1992 complete remission has occurred according to clinical hematological results: Thrombocyte (Thro) - 190x10^9 g/L; Hemoglobin (Hb) -150 g/L; Erythrocyte (Ery) - 4,6x10^{12} g/L; Color index -1,0; Leukocyte (Leyk) - 8,0x10^9 g/L; Eosmophil (Eos) – 2% Rod Like nuclei (rode. nuc) – 4%; Segmented nucler (segm) – 66%; Lymphocyte (Lymph) – 18% и Monocyte (Mono) – 6%.

2 months later (03.19.1992) the number of thrombocytes reached Thro – 235x10^9 g/L with complete normalization of blood hemapoiesis being observed: Hb - 122 g/L; Ery – 4,2x10^{12} g/L; Leyk – 6,6x10^9 g/L; Baso – 7%; rode. nuc – 3%; segm – 66%; Lymph – 18% and Mono – 6%.

Table 2 Average number of platelets at patient with chronic immune thrombocytopenic purpura (ITP).*(P< 0,05)

Year	Treatment	Mean plt x 10^9/L
June 1991	Prednisone	52
08.20-10.15.1991	Prednisone, danazol, vinblastine, IVIG**	42-52
10.29.1991	Prednisone	220
11.19-12.10.1991	Prednisone, IVIG	42-52
01.21.1992-13.19.1992	***RL-175 (170 mg/m^2)	190 235
04.19.1992-01.01.1996	***RL-175 (340 mg/m^2)	220 220

*In work [23] an example is provided of successful treatment of a patient with ITP by monoclonal antibody Retuxan (rituximab). Woman, aged 35, during 10 years underwent traditional treatment (mean plt 42-15 $x10^9$ g/L) which was unsuccessful (prednisone, cyclophosphamide, vinblastine, IVIG**, vincristine, cyclophosphorine, colchicne, azathioprine). But after two injections of rituximab in dose of 375 mg/m^2 the patient remitted (170$x10^9$ g/L). Duration of the preparation's effect is not mentioned.

**IVIG – Immune Gammaglobulin.

***RL-175 – N-phenyl-3-oxipyridine salt.

From January, 1992 to January, 1996 patient G.V. received preparation RL-175 in total dose 0,34 g/m^2 (table 2). In this period according to clinical hematological results an his objective condition the patient experienced complete and stable remission.

Table 3 presents results of how preparation RL-175 induced maturation of thrombocytes at 5 patients (n=2-6) with hereditary ideopathic TP and 9 patients with disturbed production of thrombocytes in bone marrow (n= 7-15). All 14 patients during 20 days received preparation RL-175 in total dose 150-170 mg/m^2. Frequency of objective (full or partial regress) answers was 70-90% with median duration of effect - 6 - 8 months. Effectiveness of the experimental preparation at further therapy stages was higher than 50%.

Table 3 Induction by N-phenyl-3-oxipyridine of thrombocytes (Thro) and erythrocytes (Ery) production at patients with thrombocytopenia (TP) of central and peripheral genesis (p<0,05)

Factors of TP development (n – number of patients)	**F-sex Age**	**Mean Thro x 10^9/L**		**Mean Ery x 10^9/L**	
		Before treatment	**After treatment**	**Before treatment**	**After treatment**
Idiopathic thrombocytopenic purpura:					
n=2	6	60	190	4,1	4,5
3	16	42	320	4,1	4,1
4	19	16	135	2,8	3,3
5	19	16	150	2,8	3,5
6	6	8	220	1,6	3,1
Hematosis aplasia:					
n=7	17	42	310	4,0	4,3
8	65	17	220	4,4	4,5
9	57	15	151	4,1	4,1
10	41	247	570	3,8	5,0
11	61	190	230	3,4	4,1
12	13	170	225	4,4	4,5
13	20	60	420	2,3	4,0
14	15	25	270	2,2	3,8
15	17	19	245	2,0	3,5

Clinical hematological results on TP correction of marrowy and peripheral genesis (table 2 and 3) show, that the experimental preparation has a stronger effect on proliferation and differentiation of megakaryocytic bursts (BFU-MK) than the known remedies, including Rituximab [23]. Apparently, fast growing number of hematoblasts in peripheral blood (in 6-9 times at patients n=2-9, 13-5, table 3) during 10-20 days under influence of very small doses of N-phenyl-3-oxipyridine prove high reliability of induction of endogenous TPO production. Another evidence is that in our experiment there were no abnormal sequestration (table 3 n=10-12) as a result of different time terms of cytokine receptors expression by the experimental preparation on maturation and cell differentiation of hemapoietic cells: there is data about receptors to TPO in early pluripotent stem cells, as well as late, receptors to EPO form at later maturation stages of these cells. Otherwise there would be an abnormal sequestration – speed of destruction and abnormal distribution of thrombocytes and erythrocytes in the same channel of reticuloendothelial system.

Discussion

Erythropenia and thrombocytopenia are caused by aplasia of myeloid stem cells. Their differentiation and maturation goes in reticuloendothelial system (RES). High reliability – an increase of more than 25% comparing with control values, induction of simultaneous maturation in RES of both erythroid precursor cells (BFU-E, CFU-E), and myeloid stem cells till megacarciocite with the following fast production of erythrocytes and thrombocytes (table 1-3, fig. 3) prove that activity regulation of endogenous G-CSF, EPO and TPO N–substituted 3-oxipyridine salts is being corrected. These hemopoietins are one of the most important regulators of erythropenia and thrombocytopenia [20, 23].

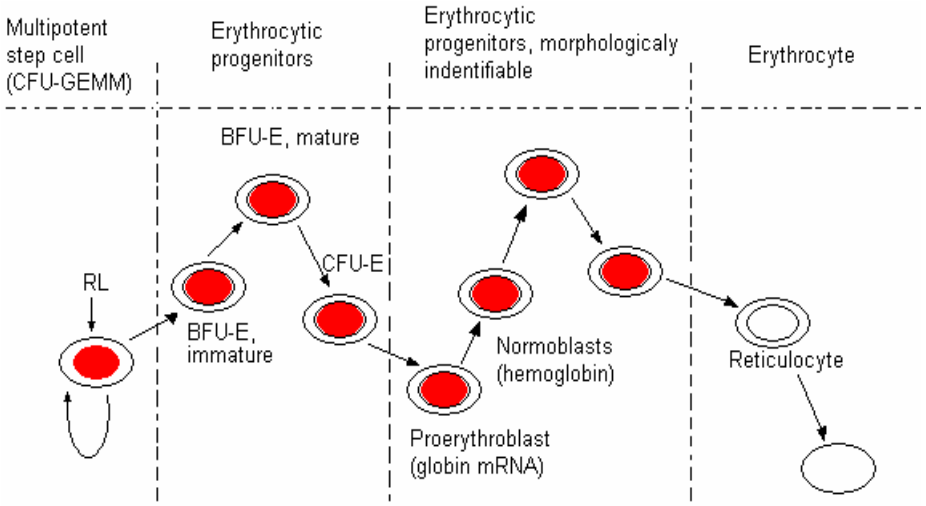


Fig.3. The major differentiation and maturation steps in erythropoiese (CFU-GEMM: colony-forming unit granulocy hrocyti, macrophage, megakaryocytic, BFU-E: burst-forming unit-erythroid; CFU-E: colony-forming unit-erythroid) [8].

The above provided experimental and clinical results are difficult to explain using classic molecular theories. First of all, it was not clear how N-hydroxyphenyl-3-oxipyridine salt activates proliferation and differentiation of normal and tumor hemapoietic cells, as it almost completely blocks DNA activity in tumor cells and at the same time inhibits RNA synthesis in these cells by 214% (fig. 2).

On the other hand, the experimental compounds considerably influence on synthesis of plasmatic ATP in normal and tumor cells, that is accompanied by activation of tyrosine kinases and growth factors, which have receptor sites to this energy currency. In this case under influence of N-substituted 3-oxipyridine mechanisms of intracellular transmission of tumorigenic signal stimulus inside the cell

nucleus should be activated in thr first turn, which our experiments do not prove [3-9, 21].

We may assume, that activation of transcriptional genes of pluripotent and then myeloid stem cells, as well as tumor cells' reverse entering into the normal cycle of cell proliferation prove an idea, that not DNA [3, 10, 11], but RNA is carrier of hereditary information. But despite looking obvious, this theory does not allow to understand how living organisms evolutionally accumulated genetic information and realise it during ontogenesis. Similar to transduction of cytokine or other signal stimuli on comlex and multivariant cascade of receptor intracellular chain, as it would require according to our calculations astronomical time of 10^6~10^7 years!

The above shown contradictions of experiment and theory could be easily overcomed if we accept a new mechanism of Watson-Crick model of genetic information transmission (fig.4).

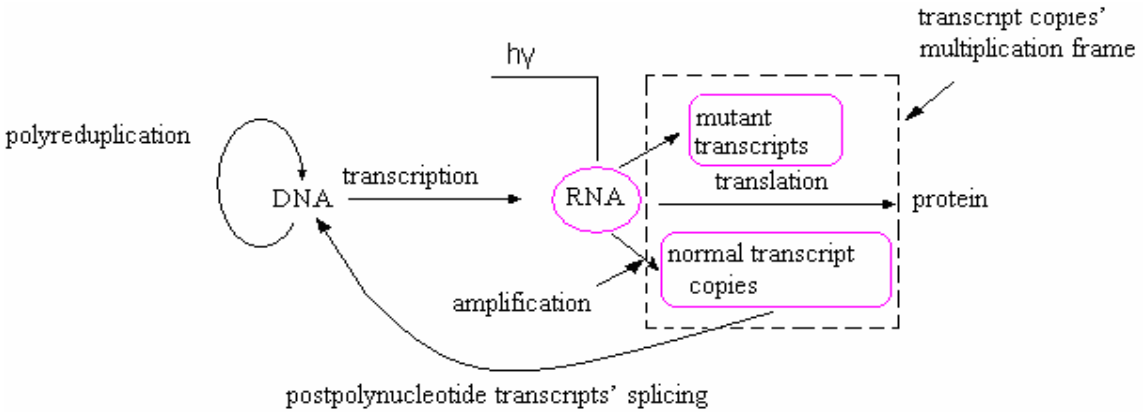


Fig. 4. New interpretation of central belief of molecular genetics, which takes into account a possibility of «edited» changes to post-transcripts and creation of new genetic information on RNA-dependant DNA-polymerases (polyreduplication). Frequency of mistakes among newly created RNA-polymerases of polynucleotide chain is 10^5 times higher, than during DNA synthesis. Reliability of RNA synthesis is achieved by numeroues copies of RNA-transcripts being made from one gene[2].

Equal levels of radiant frequancy of plasmatic ATP energy $h\gamma \approx 10^{13}$ Hz and resonant absorption of this energy frequencies ($h\gamma \approx 10^{13}$ Hz) by structural subunits of RNA-polymerases, and adequate amplifying of multiplication of normal RNA-transcripts copies and polyreduplication of newly created genetic information as a reslut of splicing of post transcripts into RNA-dependant DNA-polymerases, form a base of a new interpretation of molecular genetics' central theory.

Experimental and clinical results shown above, as well as results published in works [3-9] are reliable evidence in support of the new theory of molecular genetics. It also let explain abnormalities in inheritance of mutant trait with normal genotype at higher plants [10] and animals [11], which occur as a result of molecular mistakes during different intracellular genetic variations [2].

Experimental and clinical procedures

In experiment we used 86 cows of different age (4-8 years) and breed. Among them, according to the Veterinary Service, 20 animals were ill with hematoblastosis and 16 animals – brucellosis. They were divided into 9 groups of 10 animals (n=10) each. Healthy and sick cows divided into groups according to breed, age and level of morbidity. The animals lived in usual zootechnical and veterinary conditions of life and feeding typical in the republc of North Ossetia-Alania (Russia). Tests and observations with the cows were conducted during 7 months (term of observation). After tests animals underwent clinical examination weekly.

We also used 2 groups (control and test) of 10 healthy female Vister rats with mass of 120-150 g.

Preparation N-hydroxyphenyl-3-oxipyridine (RL-S) was injected to animals

intravenously using 0,9% isotonic solution: to rats - 3 times, $0,8x10^{-5}$ g/L and to cows also 3 times in different doses of the preparation (optimal dose $15,9x10^{-5}$ g/L) during 7 days (each alternate day).

Hematological test was the main criterion to choose optimal dose of the preparation. Results of clinical hematological research are shown in table 1. All requirements for work with laboratory animals were followed during the tests.

Cytostatic action of perchlorates N-tolyl-, N-phenyl- and N-hydroxyphenyl-3-oxipyridine (RL-3, RL-175 и RL-S) was evaluated by radiometric method [24]. Results are shown on fig.2 (a; b).

In clinic, we aprobated preparation RL-175 for 5 patients (4 male and 1 female aged from 2 to 65 years old) with acute lymphoblastic leukemia in condition of blast crisis (fig. 2d, 60-70 % blasts in myelogramme), and also 15 patients with thrombocytopenia of different genesis (table 2 and 3).

30 days after taking hormones and traditional chemotherapy (usually, CHOP) all 20 patients were treated by preparation RL-175 in the outpatient setting in hematological department of the North-Ossetian centre for Medical Bioligical problems (Vladikavkaz, Russia). Preparation RL-175 was given per os in dose of 5 mg daily during 30 days (I course). After a 5-day break treatment course was repeated depending on objective and subjective patient's condition.

Authors of this article synthesized the experimental preparations using cheap and available materials. The preparations were preclinically tested in the Oncological Scientific Centre of the Russian Academy of Medical Sciences (Moscow) and in other Russian academic centers.

Physicochemichal and biologic properties of the preparation are described in works [5,6]. LD_{16} for preparation RL-175 when given per os to rats and mice is 1200 mg per 100 g of body mass.

Criteria for evaluation wether preparation RL-175 as a mean of the last chemotherapy line had positive effect was a complete restoration of all clinical hematological and cytological symptoms of desease – normalization of blood hemopoiesis, including thrombocytes, and blast cells content in bone marrow not more than 5% given they have normal cellularity.

Clinical hematological research and exploratory puncture of bone marrow were conducted according to traditional methods. To evaluated results reliability we used Students t test.

Conclusion

Non-cytokine activation by N-substituted 3–oxipyridine salts of pluripotent stem cells' division into myeloid and lymphoid, and then accelerated stimulation of proliferation of early precursors from mixed stem colonies (CFU-GEMM), granulocytic macrophage colonies (CFU-GM), erythroid bursts (BFU-E) till their terminal maturation can substitute a number of linear specific differentiating factors: G-CSF, EPO, TPO and couples anti-gp130 MCA (MCA-agonists B1+12, B1+F1, B-S12) [13].

It is not the most important fact that the above mentioned non-cytokine stimulation of stem cells by N –substituted 3–oxipyridine salts opens new unlimited biotechnological opportunities of their creation. It is phenomenal, that experimental compounds help restore genetic program of stem cells development lost or weakened during ontogenesis and provide its normal realisation, blocking at the same time negative effect of different mutant factors. It is extremely important for Regenerative Medicine.

As you know [25], one of the main functions of gene p53 is to launch programmed cell death when the cell genome is damaged. When p53 is unadequately expressed or mutates, a program of temporary stop of cell cycle is being switched on at the G_1S–stage with the help of protein $p21^{WAFI}$. This factor predisposes to appearance of tumor cells and development of resistance to chemotherapy.

Hwang P., et al [26] revealed a new p53's function in their experiments: this gene plays an important regulatory role between glycolysis and aerobic respiration in malignant cells. Though aerobic glycolysis in tumor cells is considerably reduced, ATP concentration in these cells was comparable with norm. Blast cells' reverse entering of normal cell cycle of proliferation from dormancy (G_1S) through stage of mitosis (MG_2) at patients with ALL could be regarded as a serious evidence in

support of our new conception of cell genome activation, as well as of carcinogenesis model by Hwang P., et al.

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RNA-MATRIX OF TRANSCRIPTION AND TRANSLATION AMPLIPHICATED SPEARS OF POST-RNA TRANSCRIPTS AT HIGHER ANIMALS

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For the first time we experimentally prove the concept, that RNA-matrix of transcription and translation with prokaryote and higher eukaryote in transfer and correction of genetic stream information from one generation of posterities of animals to another.

Introduction

In 2005 Lolle S.J. with coop. [1] published proofs in favour of priority of RNA in epigenetic inheritance of an attribute in higher plants. A year later Minoo Rassoulzadegan with coop. [2] established that inheritance of mutant gene Kit in posterity of mice is defined not by molecules of DNA - conventional carriers of the hereditary information, and first of all RNA.

However in 1997 we registered the patent of Russian Federation [3] where the experimental proofs confirming for the first time was presented that carry of stream of the genetic information in higher animals reached on the RNA-matrix in a direction:

$$RNA \xrightarrow{\text{Transcription}} DNA \longrightarrow \text{Synthesis of fiber}$$

In the subsequent works from 1993 to 2003 we [3-7] provided the additional experimental results, calling in question the central dogma of molecular genetics:

$$DNA \longrightarrow RNA \longrightarrow \text{Synthesis of fiber}$$

The presented proofs in favour of model, that synthesis of fiber took place in RNA-matrix. It was based on more successful in our opinion test than in French researchers [2]. We revealed new generation of physiologically active substances (FAS) - salts N-replaced 3-oxipirid [3] which had double effect on malignant cells: practically completely oppress synthesis of DNA and simultaneously stimulate synthesis of RNA up to 214 % relatively to the control. In experiment the phenomenon close to ideology Berjamin Levin [8] was revealed, dreaming in the well-known book «Cell» (1983) to be able in vivo to provide correction and to strengthen useful attributes on the vitally-important sites genome of animals and a man.

Results and Methods

Below we show the results of examples of action of salts N-aril-3-oxipiridines for speed of introducing [3H]-timidin and [^{3}H]-urudin in the cells of line of carcinomes of human ovary on puphization of polithen chromosomes of drosophilae of low mutant line D-32, growth and duplication of barmy cells C. Tropicalis stamm CK-4, ontogenesis of drosophila, rats, mice and other results.

Example 1. We studied action of perhlorates N-phenyl, N-oxiphenyl and N-tolil 3-oxipiridinies on tumoral cells of line of carcinoma ovary of human CaO_{γ}. Speed of synthesis of DNA and RNA were estimated on inclusion of [^{3}H]-timidin and [^{3}H]-uridin in the specified cells. The estimate of citostatic actions of preparation were conducted with the radiometric way *[9]*.

The results shown in fig.1 testify the dependence of synthesis of DNA and RNA (inclusions of [^{3}H]-timidin and [^{3}H]-uridin) from structure of investigated connections.

For example, under influence of N-tolil-3-oxipiridine synthesis of DNA twice increases at a doze of a preparation of 100 mkg/ml (fig.1). This effect of action of a preparation on synthesis of DNA is kept and at lower concentration. Preparation N-tolil 3- oxipiridin at a doze of 100 mkg/ml renders partial inhibitive influence on speed of inclusion of [^{3}H]- timidin. Synthesis of DNA increases at dozes of the specified preparation of 10,0 and 1,0 mkg/ml. Connection possesses high citotoxic activity in studied dozes.

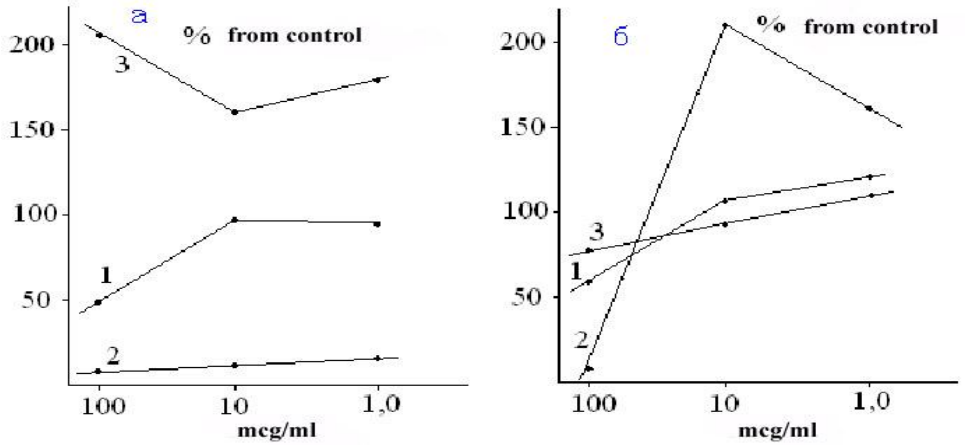


Fig 1. Dependence of inclusion of [^{3}H]-timidin and [^{3}H]-uridin in cells of lines of ovary carcinoma of a man from concentration of N-phenyl-3-oxipiridin (1), N-oxiphenyl-3-oxipiridin (2), N-tholil-3-oxipiridin (3).

Results of dependence of inclusion of [^{3}H]-uridin in cells of line carcinom of ovary of human from concentration and structures of investigated connections allows to allocate N-oxiphenil-3-oxipiridine. This preparation practically completely oppresses synthesis of DNA and simultaneously stimulates synthesis RNA considerably: inclusion of [^{3}H]-uridin increases at a doze of 10 mkg/ml on 214 % concerning a control parameter. As boundary criterion of activity 50 %-s' inhibition of inclusion of [^{3}H]-timidin and [^{3}H]-uridin at this concentration of timidin and uridin 0,5 10-3 M were used [9].

Example 2. Preparations of politen chromosomes (PC) from salivary glands of Drosophila Melanogaster was prepared with known technique [10]. The analysis of functional activity politen chromosomes was conducted with physiological card.

In allocated last the third larval age skilled drosophila F_1-and F_5 - generations of low mutant lines D-32 reared on N-phenyl-3-oxipiridin, in the fourth chromosome intensively functioning sites in the third area of Balbiani rings (BR_1) and to a lesser degree in fourth area (BR_2) within the limits of disks 4-3A_{1-6} and 4-4A_{4-6} are found out. Other three long chromosomes contain a little huge puphs with functioning up to 35 disks and more, actually passing in nucleoluse. It is possible to judge a degree of expressiveness of attributes and to following attributes: average diameter of polithen chromosomes skilled drosophila in 2 times more then control.

ПХ control animals though contain the big number of cross-section disks and the sites reminding puphs are genetically poorly active because of rather greater heterochromatic sites.

It is known [10], that intensively functioning sites in third and fourth areas BR_1 and BR_2 IV chromosomes testify to activity of formation RNA. In turn, results of research of other given I-III chromosomes containing complex puphs with functioning of 20-35 disks, actually representing nucleoluse, testify to intensive synthesis ribosome RNA on DNA nucleolus organizer [11].

Formation of a superfluous pool of pRNA (matrix, ribosome, transport and of some others) in the cell found directed mutation and steady fastening of a new useful mutation in generation

can serve as acknowledgement of an opportunity of occurrence in genome to the greater semantic information in molecules RNA than it is coded in an initial circuit of DNA. Activation under influence of investigated connections of RNA-dependent DNA-polymerase providing the return order of transfer of the genetic information means: synthesis of a circuit of DNA, on a newly synthesized RNA matrix.

Example 3. Researches of influence of N-phenyl-3-oxipiridine on growth of Candida tropicalis (16 populations) were conducted by following technique: various dozes of a preparation brought in nutrient mediums (a malt mash or the environment of Aloes) on the average in 100 repeating experiences (0,13333; 0,10; 0,0666; 0,03333 and 0,01333 mg/l). In 15 hours of incubation at 35 ^{0}C in aerobic conditions of the maintenance number of barmy cells F_1-generation in control and skilled groups counted up in chamber Gorjaeva. With the purpose of revealing of useful mutation and possible fastening in generation of an attribute in new nutrient mediums in the same sequence, as above, transferred such minimum quantity of barmy cells that it corresponded to 3-4 cells/ml. Further after incubation of cells again they were transferred on new nutrient mediums, etc., repeating this procedure with number of repeating experiences up to 10 generations (F_{10}).

In other experience to 0,5 % solution of starch and 2 ml solution of baking yeast brought of 1 % 10^{-8} mole preparation of N-phenyl -or N-ox phenyl -3-oxipiridine. The control variant differed from skilled by absence of investigated preparations in it. In 24 hours of incubation at 20-25 ^{0}C in aerobic conditions of the maintenance counted up number of barmy cells. For revealing possible fastening mutation in generation from skilled and control variants transferred on new starch solutions such quantity of cells to be corresponded in experience of 53/ml and in the control of 67/ml.

Calculation of barmy cells was conducted Gorjaeva chamber daily. Morphology of cells was investigated under usual biological microscope.

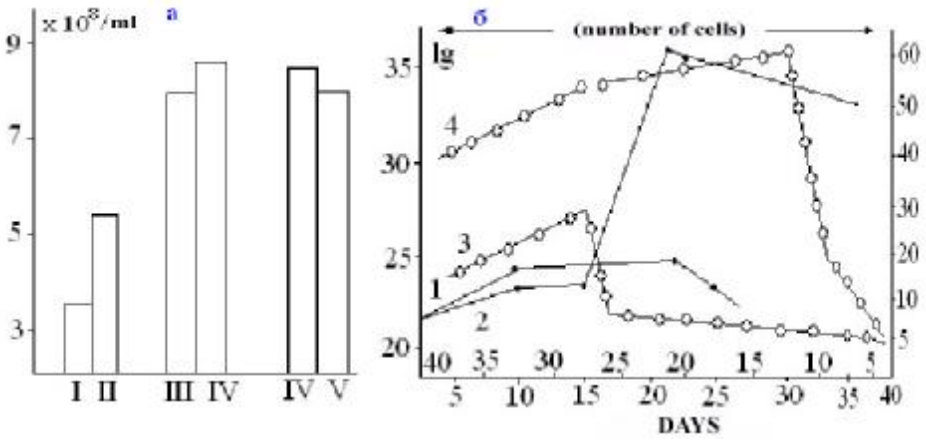


Fig. 2. Influence of various dozes of N-aril-3-oxipiridin salts on growth and duplication of barmy cultures C.tropicalis stamm CK-4. Designations: 2a-I the control, II-IV - skilled parameters of influence of dozes of N-phenyl-3-oxipiridin - 0,01333; 0,03333; 0,06666; 0,10000; 0,1333 mg/ml accordingly. 2в-1 and 2 control, 3-4 - influence 10^{-8} mole preparation N-phenyl-and N-oxiphenyl-3-oxipiridin salts on growth of population in 1 % solution of starch.

Fig. 2 presents the results of studying of influence of perchlorate N-phenyl-3-oxipiridine on growth of barmy cells C. tropicflis stamm CK-4. The action of this connection was experimented on 16 populations of cells and it was established that averagely on 100 researches of introduction N-phenyl-3-oxipiridine in a nutrient medium at optimum concentration of 0,1333 mg/l the number of barmy cells in 15 hours of incubation averagely made 834 million/ml and surpassed control populations, also incubated in a beer mash without addition of a preparation, in 2,49 times ($p < 0,001$). At the subsequent cultivation of new generations from skilled barmy cultures during 10 generations (term of supervision) in the nutrient

medium specified above without entering preparation of prolipheration of barmy cultures is kept on the average up to 1,5 times for the period of F_1 - F_{10} generations. Any changes of morphology of cells are not revealed. Synthesis of fiber for period of F_1-F_{10} of generations corresponds to speed of prolipheration.

The results of influence of salts N-phenyl-or N-oxiphenyl -3-oxipiridine on growth of colony of baking yeast on starch are presented to a nutrient medium on fig. 2b. The small number of baking yeast was inoculated in the certain volumes of starch environments. On the diagram logarithms of growth and cell fission with constant speed exponential phases are found out. Yet the exponential growth phase of baking yeast under influence of N-oxiphenile-3-oxipiridine within 30 days considerably higher to similar growth phases for control groups.

The inoculation of a small number of skilled and control eukaryote on new starch environments showed higher (on two and more orders) speed of cell fission in experience.

At entering N-phenyl-3-oxipiridine environment containing baking yeast on starch diet, the certain period a log-phase is found out (time of cells fission) with the subsequent explosive growth of colony of cells (figs. 2d: 3-control, 4-experience). It is important to note, that under influence of investigated connections the speed of division of skilled eukaryote after a log-phase explosively increases, surpassing a control parameter in tens, hundreds and thousand times, and this high speed of prolipheration was fixed during the long period of time (60 days - term of supervision).

In usual conditions barmy cells do not utilize starch. The significant explosive growth of colonies of baking yeast only on starch environment testifies to the directed mutation of genome cells aside to metabolism of starch.

Example 4. In research not pathogenic culture of intestinal bacilli E. coli and its three pathogenic stereotype - 026, 0119 and 0144 were used. They were allocated from clinical material of North-Osetiya republican children's hospital. All used bacteria concerned to stable recombinate R.

Influence of investigated connection on overcoming resistance of infectious stable recombinate microorganisms E. Coli defined in relation to following antibiotics: neomycin, monomicin, penicillin, chlortetracycline, erythromycin, oxithetraciclin, streptomycin, tetracycline, levomicin.

Definition of sensitivity to antibiotics was conducted by the standard techniques: diffusion in agar and serial cultivations in broth. The material in regular intervals distributed on a surface of environment. Cups dried 30-40 minutes at a room temperature, then on a surface environments imposed disks on uniform distance from each other and on distance of 2 cm. from edge of cups. Cups with disks maintained 30-40 minutes at a room temperature and further 16-18 hours at 36-38^{0}C.

The estimation of influence of perchlorates N-phenyl-, N-oxiphenyl-and N-tholil-3-oxipiridine was conducted on diameter of growth inhibition of colonies around disk, including diameter and the disk itself. The more the zone of a growth inhibition of experimented cultures, the higher its sensitivity to the given concentration of antibiotic: up to 10 mm sensitivity accepted for insensitive. While testing the preparations 24-hour broth culture was used. For its cultivation nutrient medium was used with following dozes of antibiotics, mg/ml: 200,0; 20,0; 2,0; 0,2; 0,02; 0,002; .0,0002; 0,00002; 0,000002; 0,0000002.

Table 1 shows the results determining the sensitivity of not pathogenic (I) and pathogenic stereotypes E. Coli 0119977 (II), 0144886 (III) and 026028 (IV) to antibiotics. From the resulted results it is visible that E. Coli is resistant to influence of all nine investigated antibiotics.

Table 1. Sensitivity of not pathogenic and pathogenic stamms E.Coli to antibiotics under influence of salts N-phenyl-, N-(n-oxiphenyl) - and N-tholil-3-oxipiridin.

Culture of a bacterium	Antibiotics								
	Neomycin	Monomicine	Penicillin	Chlorine-tetracycline	Oxitetracicline	Streptomycin	Tetracycline	Erythromycin	Levomicine
Zone of sensitivity, mm									
The control	n/h	n/h	n/h	n/h	n/h	n/h	n/h	n/h	n/h
Not pathogenic E.Coli	30 24 23	23 20 23	19	20 14 28	20	22 24 21	26 25 20	30 25 31	24 25 24
Pathogenic stereotype 0119977	27 24 35	25 23 30	30	23	30 25 40	28 23 40	30 22 30	18 30 30	20
Pathogenic stereotype 0144886	24 17 40	30 20 40	30 40	40	22	25	26 22	37	19
Pathogenic stereotype 026028	13 30 18	18 14 15	14			20	18 14	20	20 15

If to consider the diameter of zones of growth inhibition of culture, as the test for biological activity under influence of investigated connections not only stability is overcome, but also sensitivity of pathogenic and not pathogenic cultures antibiotics at 20-40 time that associates with blocking activity of amplificated gene and, hence, coding of glycoprotein increases.

Practical value of received data has been confirmed in experiment on monkeys macaques-rhesus factors Macaque mulatta suffering from recurrencing dysenteric colitis. N-phenyl-3-oxipiridine (the Report of Institute of an experimental pathology and therapy of Health Academy of USSR, 1981) is proved as a high adaptogene and therapeutic effect.

Example 5. More than 10000 individuals of low mutant lines D. melanogaster D-32 and fruit drosophilae of wild line (Berlin wild) were used in work. Virgile D. melanogaster lines D-32 for crossing in pairs 3♀ x 3♂ were placed in separate test tubes in diameter of 18 mm during 48 hours. Parental pair (PP) was deleted and their posterity passed its development from an egg up to imago on a forage from agar, raisin and semolina with various dozes of perchlorate N-phenyl-3-oxipiridine. Control group was fed with a forage without preparation. From one-age flies F_1 were made by new families. One part of PP_1 was fed with a forage with various dozes of perchlorate (group I - 0,05 г; group II - 0,10 г; group III - 0,15 г and group IV - on 0,20 г in 100г forages). Other part of PP_1 has been transferred to a forage without preparation (N). The flies received from last PP_1 were designated as F_2. Under the similar scheme we received F_3 and F_4 generation. Flies contained in thermostat at 25 ^{0}C and each 10 days replaced to a fresh forage. Daily we spent fixing duration of development of stages: time of occurrence of maggots (M), chrysalises (C), imago (I) and quantity of hatched flies. Results are given in tab. 2.

The research of the picture of puphing (table.2) was conducted in F_1 and F_5 generations of larvae of the third last age crept out of the forage and slightly dried. Influence of conditions of environment, the age factor and other parameters have been shown, whenever possible, to a minimum.

In other experience, selected in the casual order virgin flies for their third day of imaginal lives were placed in pairs 3♀ x 3♂ in separate test tubes for crossing during 48 hours then the parental pair PP was deleted. The new generation of flies passed all cycle of development on the environment with various dozes of N-phenyl-3-oxipiridin. The received flies were marked as F_1. By a casual choice the

new parental pairs were selected from virgin flies of the first F1 generations. One part of PP_1 was transferred on normal (without preparation) forage and another was placed on a forage with the same dozes of preparation as above,. From F_1 in the same way depending on the maintenance on a normal forage (N) or on a forage with a preparation (A) we received F_2 – imago generations, and further from F_2 F_3 - F_5- generations. Every 7-8 days flies were replaced to a fresh forage. Virgin one-day flies were used in all variants of experience contained in thermostat at temperature 20 ± $0,1^0$ and 25 ± $0,1^0$ and 30 ± $0,1^0$C. The account of the lost flies conducted daily.

The minimal and maximal life expectancy of control F^1 generations at 25 ^{0}C made for females 34 - 50 and males 37 - 49 days, and at 20^0 and 30^0 - 22 ± 1,0 and 10 ± 1,5 days accordingly (P< 0,001). In work the results were used in which basic concurrence of several repeated experiences were observed.

In table. 2 the results of cultivation of parental pairs D. melanogaster a wild population on N-phenyl-3-oxipiridin forage are given. From the presented data follows, that in experimental conditions of their maintenance (20^0C or 30^0C), i.e. in conditions when synthesis except for fiber of a thermal shock in the organism of drosophilae completely stops, the powerful F_1 generations of flies on the whole complex of attributes (P< 0,001) is observed: reduction of development of a cycle from an egg up to imago on 30 - 35 %; increase in length of a body at 10 %; the density of population increases in 2-4 times; average and maximal life expectancy has grown on 110-160 % concerning the control parameters fixed in F_1 - F_5 generations (term of supervision). The lead experiment is explainable from the point of view of influence of investigated connections on alarm sites of genes of drosophila ontogenesis.

Table 2. Influence of N-phenyl-3-oxipiridin on ontogenesis of D.melanogaster of wild population for the period of five generations (F1-F5) in extreme conditions.

Temperature, ^{0}C		On a forage	Difference concerning the control, %			
			Reduction of a cycle from an egg up to imago	Density of population	Average life expectancy	The maximal life expectancy
20	F_1	A	30 – 35	116	114	140
30		A	30 - 35	224	110	163
20	F_2	A	12	23	0	14
		N	27	47	8	12
30		A	24	19	50	22
		N	30	50	18	10
20	F_3	A	0	40	22	22
		N	17	50	10	27
30		A	10	36	22	11
		N	30	67	10	9
20	F_4	A	12	28	30	13
		N	19	43	20	16
30		A	25	14	60	11
		N	36	47	30	0
20	F_5	A	27	50	62	21
		N	30	31	71	52
30		A	10	30	23	11
		N	17	101	31	52

Example 6. The nonlinear rats, rats of line and mice were used in work. For research of influence of salts N-phenyl-and N-oxophenil-3 oxipiridin on generative activity and an opportunity of artificial regulation of a parity of floors of animals selected by a principle of pairs-analogues in view of age and alive weight. 70 rats of both sex used in experience. All

animals were divided into three groups in pairs (male-males). The parental pairs were placed in separate cells where they were during all experiment (before reception from these pairs five generations of posterities) in identical conditions of usual feeding, water mode and the maintenance in vivarium. The animals of control group (1) in quantity of ten pairs "families", coupled with males and females of six month age in weight 180-220 g. The animals of the second group consisting of 10 pairs of "families", males and females of six month age in weight 180-220 g. for 38 - 40 days before pairing were fed by N-phenil-3 oxipiridin by peroral introductions through the probe in the form of spirit solution in dozes of 10 mg daily, 1 time per day within 15 days. In the third group of 8 parental pairs similar age and weight, as in groups I and II. The male was fed with investigated preparation in the same dozes before 38-40 of pairing. The experiences were conducted for control and skilled groups of animals in April - May - September when the parity of sex on literary data [12] makes male-female, %: 50/50; 42,2/57,0; 45,0/55,0 accordingly.

From results of research of influence of N-phenil-3 oxipiridin on puberty, the occurrence of offspring, the weight of testicles and appendages of rats, and also the parity of weight of organs to weight of a body and mixture of parity of sex can be concluded that the rats born from parents fed by preparation, both in group II and in group III acceleration of true puberty on 38 - 26 days is revealed, terms of occurrence of the first testicles are reduced from 116-118 days in the control over 80-89 days in skilled groups, i.e. to 27-26 days.

The account of testicle in "families" were conducted within 92 days from the moment of the first testicles as this term makes average time of an interval between testicles at control rats.

For the specified period in ten control "families" (group I) the offspring made 119 rats, whereas in ten skilled "families" (group II) - 239 rats, and in eight "families" of group III - 203 rats, in five "families" of group IV – 56rats. The recalculation of one pair the quantity of rats is made by group I - 12; group II - 24; group III - 25; group IV - 11 rats. Thus the population growth goes not due to increase in individuals in offspring, but due to reduction of intervals between offspring and increases in quantity of offsprings: in group I (control) average time of intervals between offspring makes 92 days (disorder of 90-96 days), group II - 36 days (disorder 27-45), in group III - 36 days (disorder of 28-49 days) and in group IV - 94 days (disorder of 90-99 days).

The increase of fruitfulness in twice and more of nonlinear rats due to reduction of intervals between offsprings, and also occurrences of early puberty under influence of N-phenyl -3 oxipiridin was observed during five generations.

For the period of supervision we did not note appreciable ageing of reproductive function of rats. Physical development rats born in skilled families, within the first month postnatal lives did not differ from control: after 24 hours of birth the weight of rats in control families made 6-8 g.; in families of group II - 6-7 g.; groups III-7-9 g.; groups IV – 7-9 g.

The increase of weight, disclosing of eyes, cover of fur at rats in skilled families goes according to physiological specifications.

The analysis of metaphase of plates of bone brain of rats has shown, that chromosomal aberrations are absent, all chromosomes are achrocentric, normal, spiralization is not broken.

The experiment proved the presence of linear dependence between influence of N-phenil-3 oxipiridin on activation of testicles and their appendages that is shown in fast and intensive growth of their weight exceeding weight of testicles and appendages at control rats of the same age and weight (table .3) is proved.

Table 3. Influence of N-phenyl-3-oxipiridin on weight of ovary glands and appendages of rats of various age and on a parity of weight of bodies and weights of a body (10 units in group).

№	Structure of groups	Weight of testicles and appendages of rats of different age, mg					
		47-51 days			4-6 months		
		Testicles	Append-ages	Parity of weight of glands to the weight of bodies	Testicles	Appendages	Parity of weight of glands to the weight of bodies
I	The control (intact)	560,0±63,2	67,0±4,4	4,8±0,4	1200,0±93,1	110,0±10,5	6,5±0,5
II	The control (physiological)	555,0±38,5	48,0±2,5	5,0±0,5	1200,0±44,5	92,0±9,6	6,6±0,4
III	Experience	700,0±18,3	21,0±6,2	7,8±0,8	2077,0±64,7	183,5±6,3	8,3±0,4

The histological research of testicles of rats painted on Felgen and Brache has shown substantial growth of thickness of testicles up to 250-320 microns (in the control 150-200 microns), increase in all layers sperm tissue and also quantities actively mobile of spermatozoa (tab. 4).

Table 4. Parameters of function of testicles of matured rats.

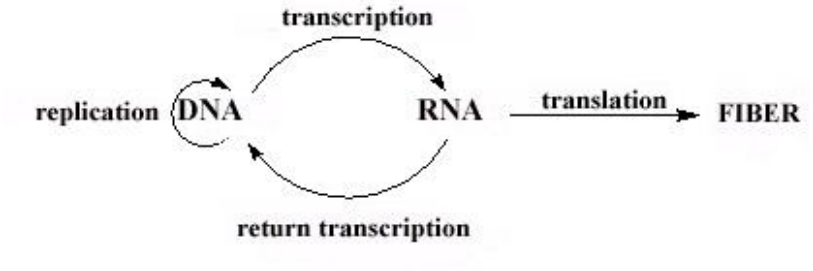
Parameters	Groups	
	Skilled	Control
Quantity of layers of spermatogenesis epitel		
1. spermatogone	1	1
2. spermatozoa - I-II orders	4-5	2-3
3. spermatid	6-7	3-4
Quantity of forming spermatids on 1 cell		
1. Sertoli	40-60	15-20
2. In % to the control	267-300,0	100,0
Mobility of spermatozoa in % 1.		
1. In four hours	60,0	45,5
2. In twelve hours	33,3	28,0
Quantity of motionless forms of spermatozoa in %	21,0	25,0
Quantity degenerative changed spermatozoa, in %	7,2	8,0

Leidig cells producing man's sexual hormones and supporting spermgenesis are functionally active, it is expressed in increase in volumes of kernels, their general sizes in comparison with the control. Nuclear-citoplazmatic parities are within the limits revealed in control rats.

Conclusion

The model of a double spiral of DNA and realization of the genetic information incorporated in it through a transcription and translation is considered a universal code for all alive organisms [8]. Detection in 1970 G.Temin and D.Baltimor [8, 11] in virions of swelling

RNA viruses containing enzyme - return transcripnaze capable to synthesize RNA allowed to formulate finally the central dogma of molecular genetics under the following scheme:



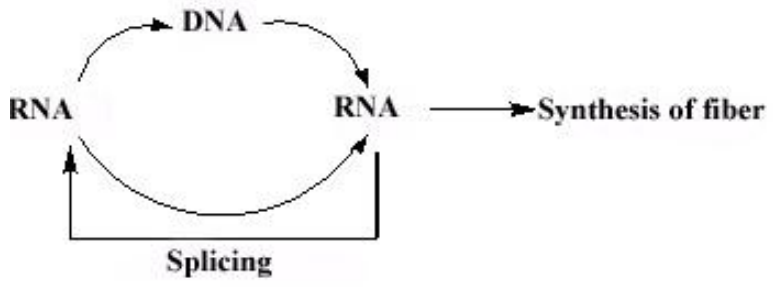
However we [3-7] publish a series of works where the experimental proofs denying the standard central dogma of molecular biology have been presented. In particular, in the patent of the Russian Federation (1997) we[3] revealed at studying of influence N-replaced oxipiridin for speed of synthesis of DNA and RNA in tumoral cells of line of carcion ovary of person Caγ is registered: practically at full oppression of synthesis of DNA there is a simultaneous stimulation of synthesis of RNA up to 214 % concerning a control parameter (figs. 1).

In politent chromosomes of skilled low mutant drosophila D-32, fed unitary with N-phenyl-3-oxipiridin in 4-th chromosome intensively functioning sites in the field of $КБ_1$ and $КБ_2$ are found out. Other three long chromosomes contain a little huge puphs actually passing in nucleus. These morphogenetic characteristics testify also of intensive synthesis information RNA under influence of investigated connection.

The experimental results received by us allow apparently to conclude that the investigated N-replaced salts of 3-oxipiridin render significant influence on activation of RNA-polymerase. In particular this activation is shown in amplification and duplication of a copy semantic in norm of RNA-transcripts.

Significant influence in vivo on processes of "editing" at the higher animals, i.e. occurrences of the big genetic information in molecules of RNA than it has been coded in initial molecules of DNA, also testifies to influence of investigated connections on splicing mechanisms.

Thus, from the above-stated experimental material it is possible to conclude that the direction of distribution of the genes information occurs on the mechanism of return central dogma of molecular genetics from RNA to DNA where on a matrix information мRNA synthesis of fiber at the maximum animals from one generation to another during embryogenesis is carried out



The role of RNA in inheritance of features was proved in higher plants and animals. Though inheritance of high percent of posterity with white spots on paws and a tail in mice with normal genotype Kit $^{+/+}$ at various genetic variations on crossing with each other of wild genotype Kit $^{+/+}$ (responsible, besides other, for formation of a dark pigment of melanin) with heterozygote (genotype Kit$^{+/-}$) and homozygous (Kit$^{-/-}$) animals, cannot serve as the unequivocal proof of role of RNA as matrixes in transferring of the genetic information to posterity. It is not excluded, that duplication of a copy of mutant post RNA - transcripts is defined supervised) both overlapping Kit with other genes, and other factors.

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Materials of the Conferences

THE EFFECTIVENESS OF USE SMALL FISHES AND FISHES OF LITTLE VALUE AS STERN WHEN MANUFACTURING OF STURGEON ACIPENSERIDAE

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Amongst the fundamental biological problems the main is the problem of natural and artificial reproduction of fish at sea and freshwater reservoirs.

In Azov and Black Sea basins the reduction of the general catch and change of proportions valuable and fish of little value has been existing since the middle of 20th century. Against the background of the reduction of production of a small fish volume, earlier referred to little value, started to form a new base, such as: sardelle Clupeonella delicatula, black sea Sprattus phalericus, Azov khamsa Engraulis encrasicholus maeoticus and others. In recent years the catches of Azov sturgeon have sharply decreased from 1228,4 ton (in 1984) to 158,6 ton (in 1999). And it continue to be on extremely critical level, not providing natural reproduction, in spite of introduction since 2000 moratorium on the industrial catch of sturgeon type of fish.

In relationship with reduction of the catch of sturgeon kinds of fish in natural reservoir, the problem of sturgeon production leaves on the first plan of the development of aquaculture as a whole. The development of manufacturing of sturgeon supposes not only the reception of sturgeon for sale using different methods of growing (in ponds, fish tanks, pools), but also making and conservation of the uterine live-stock of sturgeon fish, searching for the most efficient objects for breeding, but all these problems comes to the global program of the conservation genetic resource – the genofund of sturgeon (Nikitina, 2003).

One of the conditions of making success in breeding sturgeon kinds of fish is providing growing fish with provender of good quality. At present recipes of domestic mixed fodder are created with fish meal with different additives (Kiselev and others, 2004; Golovin, Korabelinikova, 2004; Denisenko, 2005; Voropaev and others, 2006). Many import additives are also used. But breeding sturgeon fish becomes unprofitable because of their high cost.

The most simple and efficient type of stern for sturgeon is the mincemeat made of fresh or frozen fish (Zhukovskiy, 1965; Burcev, 1965; Romanycheva, 1973; Abaev, Dorofeeva, 1979; Nikitina, 2003). Fish used as stern - the most balanced provender for sturgeon kinds of fish and it is also the main type of food for the majority of fish in the natural environment.

In our opinion, there are no problems with fish provender in the south Russia in Azov and Black Sea pool, where fish manufacturing enterprises and private enterprises annually gain about 38 thousand ton of little value type of fish and small Clupeidae. Moreover this catch is realized for the whole year. The cost of stern fish is low: 4 - 4,5 rub./kg or on official course rate of the Central Bank to Russia on 1.04.2006 0,1444 - 0,1624 $ /kg or 0,1189 - 0,1338 €/kg.

Therefore breeding sturgeon fish was conducted with using as stern little value freshwater fish, small Clupeidae and sea type of fish of little value.

The studies were being organized in the ponds (the area of each pond - 0,1 hectares) during three years. The objects of growing for sale were “burtsevskaya” Huso huso x Acipenser ruthenus and “vnirovskaya” Huso huso x (Huso huso x A ruthenus) and beluga Huso huso.

2-year sorts of ”burtsevskaya” at the end of the vegetation period had an average mass 800 gram, sorts of “vnirovskaya” - 1140 gram, belugas - 1400 gram.

3-year sorts of “burtsevskaya” at the end of the vegetation period reached the average mass 1990 gram, of “vnirovskaya” 2010 gram, belugas - 2200 gram.

The stern expenseses for breeding sturgeons by fresh fish were no more than 5,0 kg/kg increase.

We have got the result that physiological factors of the condition of surgeon (Nikitina, 2005) during the breeding have confirmed the

conclusion: this intensive method of growing surgeon fish for sale in pond with using fish of little value and small-herring type of fish as stern helps us to get product of a high quality. Using only the part catch, in fish-breeding and farming facilities it is possible to get about 10 ton/ha goods sturgeon of fish.

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RESEARCH OF NATIONAL EDUCATION PROBLEMS IN THE YENISEI PROVINCE IN THE BEGINNING OF XX CENTURY AND THEIR ADAPTIBILITY FOR THE PRESENT STAGE OF RUSSIAN REGIONS' DEVELOPMENT

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In the clause the system of parameters describing a social status of national teachers of the Yenisei province in the beginning XX century is considered: the living wage, prosperity, security habitation, dwelling and occupied places accomplishment level.

Estimating the social status B.V. Rakitsky allocates the system of parameters, where there is a cost index of life (living wage, prosperity, etc.), security habitation, dwelling and occupied places accomplishment level, etc. [5, p.21]

When speaking about social and economic problems of a region, first of all the problems in the sphere of education are paid attention to.

The Yenisei province was one of the greatest territorial parts of Russia and one of the most removed ones from the center that presented considerable difficulties for the province's inhabitants and for carrying out in practice state reforms in the end of XIX – beginning of XX centuries. The enormous spaces of Siberia with its imperfection of a transport network were a noticeable barrier on the way of involving the region into all-Russian economic relations.

The communication between settlements inside the districts was performed in general by country roads, which condition was unsatisfactory, despite of considerable means appropriated to their maintenance. Up to the end of XIX century the only one transport artery leading to the European part of the country, was the Siberian Highway (Sibirsky Trakt). Inside the region the passage between Minusinsk and Achinsk was the busiest one. The grain trade from Minusinsk district to northern volosts of Achinsk and Yenisei districts and also to Tomsk province was carried out there. [3, pp.162-163]

The presented below table 1 shows the price ratios for the basic food stuffs in the Yenisei province.

Table 1. Prices for the articles of primary necessity established for the Yenisei province cities, 1915 [1; 2]

Articles	City				
	Krasnoyarsk	Achinsk	Minusinsk	Yeniseisk	Kansk
Rye bread, baked, a pound	2.5k	-	-	-	3 k
Hemp oil, a pound	16 k	16 k	12 k	16 k	18 k
Butter	37 k	-	-	-	35 k
Eggs, a hundred	1.55 rub	1.60 rub	1.10 rub	1.80 rub	1.30 rub
Stearin candles, a pound	40 k	40 к	40 к	42 к	40 к
Matches, a box	2 к	2 к	2 к	2 к	2 к
Kerosene, a pound	7.5 к	7 к	8.5 к	8 5 к	8 к
Beef, a pound	10-13 к	11-13 к	9-11 к		11-13 к
Veal, a pound	12-15 к	13-15 к	10-12 к	12-15 к	11-12 к
Lamb meat, a pound	9-11 к	9-11 к	8-9 к		8-9 к
Pork, a pound	10-12 к	12-13 к	9-10		10-11к
Loaf sugar, a pound	21 к	21 к	21.5 к	22 к	22 к
White sugar, a pond	18 к	18 к	19 к	19 к	19 к

Analyzing the given tables and comparing them with the salary of teachers in the Yenisei province - 360 rubles a year, we shall note a hard financial situation of national education workers. For each 5 years of work the basic salary of a teacher carried an extra charge of 60 rubles. Thus, a teacher having worked 20 years, had a salary of 600 rubles. An increase of 120 rubles for the work in severe conditions of the Yenisei province was assumed also. Thus, more or less worthy wage could be only given to a teacher who had worked not less than 15 years. But young teachers and those having greater families had the salary that "did not make any satisfaction considering all the modesty and skill to live of national teachers ". From pages of newspapers and magazines the Yenisei province teachers addressed to the government with the request "to pay attention to earnings of national teachers especially in Siberia as he has to struggle for life existence even more here" [6, p.45]. Under these circumstances in the sphere of National Education, in the beginning of XX century the Yenisei province teachers were not sure of tomorrow, did not see any prospect to improve their life neither in the economic nor in social spheres and left work at school. According to the Siberian School Census, 1911, the teachers having served less than 5 years made up 57 % from the general number of the teachers; from 5 till 9 years - 26 %; more than 9 years - 17 % [6, p.46]. The young men, being educated and feeling forces for any beginning, having got no satisfaction in a teacher's field, tried to find another job which would allow creating better conditions for life.

The high level of dwelling accomplishment and security habitation of the Yenisei province teachers in the beginning of XX century is not worth speaking about, either. The apartments which were given to the teachers, especially in countryside, were far from ideal ones: old construction and demanding repair houses not adapted for life economically, the temperature in the apartments in winter was

low. The teachers' habitation problem was discussed at Pedagogical Congresses and in press. In "Siberian school (Sibirskaya Shkola)" magazine, 1916, some clauses where the housing question was mentioned and the teachers described their life were published: "water in the samovar freezes…It is necessary to go to bed in clothes, … the oven burns badly, because the fire wood brought from a bog is damp" [7, p.76]

On the basis of the above-stated, we can draw the conclusion, that the parameters of the social status of the Yenisei province teachers in the beginning of XX century left much to be desired. The problems mentioned in the clause are urgent for the modern condition of economy and education as well. Now the financial situation problems of a teacher are far from being

satisfactory, too. As well as in the beginning of XX century the solution of problems of payments for the National Education workers, increase of their social status, and the establishment of a worthy living standard for them is required.

The alignment of regions' development conditions was and remains in the center of attraction as the precondition of market relations' and social infrastructure reforming. In conditions of market economy the system of the state guarantees and indemnifications for northerners requires a transformation on the basis of the differentiated approach to the workers employed in the budgetary sphere and in non-budgetary sector of economy. The basic state guarantees and indemnifications for the working and living in northern regions are: regional wage factors and rated increase [5, p.663]

The investigated facts were the objective base for the solution of problems of National Education on the boundary of XX century that remains urgent also during the present period of the development of Russia. It proves the necessity of studying and using rational ideas of that time for the solution of National Education reforming problems of the present.

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Materials of the Conferences

"THE CUPOLA ALGORITHM" DATA AND "THE MODULATION-37" THE NATURAL SCIENCES ASPECT AND THE USING FOR ANALYSIS OF ANCIENT LAYOUTS

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The measure and proportional analysis of the historical monuments is probably the most famous problem in the historical, archeological, metrological and architectural researches from antiquity to nowadays. Such names as Alberti, Choisy, Le Corbusier, Dürer, Gioltovsky, Hambidge, Palladio, Plato, Rybakov, Vioillet-Le-Duc, Vladimirov, Vitruvius, Zeising and many others may be mentioned in this connection. This article is devoted to the same questions. The developed original methodology is based on the specific integer data having sacral origins. These data were discovered by the author as a result of analysis of some well known integer archetypes from European and Asian traditional cultures (they are sacral integers "dalkha" from Tibet mythology; sacral Moon days numbers devoted to Lu-Ban, the China divinity-protector of carpenters and builders; and, especially Orthodox "cupola canon", including the data ***1, 2, 3, 5, 7, 9, 13***). That's why we named the integer process, generating these data, "The Cupola Algorithm". The continuation of the sequence was produced with addition of 2^n to the previous term, thrice without changing this addend, and increasing ***n*** by ***1*** after every third step, and so on. So, the degree of ***2*** was constant for every 3 steps and was increased before every 4-th step. The result is: ***1, 2, 3, 5, 7, 9, 13, 17, 21, 29, 37, 45, 61, 77, 93, …***

Indicated sequence has some noteworthy properties, but the most interesting one is its coming to the data of the Titius-Bode rule, with very simple procedure: it's enough to add ***7*** to every third term: ***3+7=10*** (Earth); ***9+7=16*** (Mars); ***21+7=28*** ("Phaeton"); ***45+7=52*** (Jupiter), etc.. There are some reasons to take note of the 11-th term 37 (look through our previous published works), for instance to compare it with the sacral quality of Burma divinities called "*nats*". These considerations allow us to suppose existence of the integrated ancient module-unit, which was equal to the simple (base) unit multiplied by 37 (this measuring principle named "The Modulation-37"). These regularities were used in some executed researches, concerning the measures and proportional characteristics of the number of ancient layouts (Babylon, Great Pyramids in Gizeh, Athens and others), with the aid of special elaborated program modules. Foot was used as the base unit. Founded, as a result, "chains", "trees" and '"loops" of dimensions have the layouts significance and the logic interconnections in the Cupola Algorithm and Modulation-37 sense, so our analysis methodology may be declared as a quite adequate.

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COMPETENCE - BASED APPROACH IN HIGHER SCHOOL EDUCATION[1]

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The problem of exploration of the structure of inner essence of notion "competence", defining the key and special kinds of modern specialists' competence is an actual, vital and perspective today. Firstly thanks to the fact that nowadays labor market demands not only to knowledge of specialists but to their competence.

If seems to us that joining Russia to Bologna agreement is also an important argument, as it determines necessity of using common language, terminology with help of

[1] The exploration work is carried out with financial help of the Russian Humanitarian Science Fund and the Government of Astrakhan region (grant № 05-06-31603 A\U).

which it'll be possible to describe the educational process, its goal and results in particular.

More over forming competence as an integral personality's foundation needs creating and using new active and personal oriented technologies. The competence approach itself to the goals and results of Higher Professional Education, even on the stage of scientific and practical development and testing takes a decent place as a system of methodological instrument in organizing of educational process.

In our investigations we explore competence itself and competent abilities as mutual and subordinate component of subject activity. We intend to examine the competence as a potential activity, disposition and aspiration to the concrete kind of activity. Competence is an integral quality of a person, which is successfully realized activity. Components of competency in any sphere of life activity, in our mind, can be introduced as those:

- Cognitive component (knowledge)
- Motivation component
- Axiological component (trend and valuable relation of personality)
- Behavior component (skills and experience)
- Abilities
- Emotional and willing components (self regulation).

In this case competence is considered to be as potency of competence that can be realized in the definite sphere of activity and must become valid with the help self-organization self-regulation mechanisms.

To evaluate the professional and socio-psychological competence of a man we need a complex approach, which suggests taking into consideration inner (subjective criteria of competence):

- Sapid characteristic that is a complex of inner inducements, purposes, motives of behavior and activity, direction of interests, etc
- Level and quality of results that is of those real achievements got as result of man's activity
- Peculiarity of a procedure of activity, such as tempo, speed intensively, volume.

Outer (objective) criteria of disposing man's competence are:

- Degree of expressed inner motives, want to activity, aspirations to overcome undertaken actions and abilities
- Rate characteristics of reactions and operations
- Variation of methods action used in (doing) fulfilling proposed tasks.

Competence of a higher education graduate as a future specialist contains in its kind structure professional competence (readiness, intention to work in definite professional sphere) and socio-psychological one (intention and readiness to live in harmony with oneself and other people, in the harmony with one's individuality and social environment. However, in its turn each of these competences can be divided into general basic, key competences common to all graduates of any higher education establishment. The structure of competence surely consists of 4 blocks of competencies:

1. General professional competence.
2. Special professional competence
3. General socio-psychological competence
4. Special socio-psychological competence.

General professional competence includes competence in the sphere of science and exploration, project and construction, administration, management, production and education activities.

General socio-psychological competency is represented by social, personal, in formative, ecological competence and others.

Special professional competency or qualification is a degree or a kind of professional training of a graduate, his possessing of professional competences (those are his readiness and motives), required for fulfilling definite professional activity. His competence is determined by state qualification characteristics.

Special socio-psychological competence represents readiness and ability to mobilize professionally important qualities ensuring production of direct specialist's activity. In today's scientific, pedagogical and psychological literature there are a huge number of tendencies in the problematic field of realization, the most important of which can be grouped around:

- Active forms of teaching (problematic lecture, seminar-discussion, role-playing and others).
- Creating profession-developing situations when a student must demonstrate personal professional position.
- Dialogical type of communication.
- Professional positioning.
- Contents of specialist's model concerning competent approach to the goals and results of higher professional education
- Taking into account the definition of competence as an integrative quality of a person which represents unity of motive axiological, cognitive, behavior aspects of his abilities and other professionally important qualities of top specialist's educational system should be directed of these components.

While investigating the problem of forming competences in the establishments of higher education we were interested in studying the teachers' notions on this theme as they are subjects of educational process.

According to the results of questioning the teachers use different notions and meaning in definition "competence of the higher education specialist" the majority of high school teachers don't take the notion "competence" clearly, it is not structured in their minds and, accordingly, if can't serve as really imagined goal of their pedagogical activity. It leads to the fact that competence of a future specialist is being formed chaotically, out of definite goal reaching in the logically organized pedagogical process.

We believe that definite measures on the way of perfecting of the educational process can be done through work of cathedral scientific methods seminars, the aims of which is development of professional competence of the teachers of the chair.

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THE MODEL OF ECOLOGICALLY BROUGHT UP PERSON

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Ecology as a concept in recent years has become integral, and was enriched by new information and become a science, which touch on all spheres of economic, social and spiritual of a human and society. As its final aim and functions ecological education nowadays is inevitably connected with social life of people. It will be effective only iff all members of society take part in decision making that concerned with the improvement of relations between people and the environment. That is why, talking about specialist's competence, besides the technological training, usually it is meant by this a number of components, which may include parts of any kind:

1. Psychological (tolerance, openness, optimism, intuition, resistance to stress),
2. Intelectual (creativity, observation, criticism, integrity of thought, reaction time),
3. Behaviour (enterprise, responsibility, riskiness).

Let us deal with a project of a model of a graduate of technical type – a specialist for the social labour market. It is very necessary for the successful realization of such a model to have the effective interaction of two fields – macro-field, which is the State and all groups of educational structures and their correlation and social and industrial field, that forms its demand sometimes incorrectly, especially at the period of revolutionary economic reforms.

There are a certain number of characteristics any specialist must have for different kinds of activities:

Interpersonal characteristics:

– Ability to organize the process of communication;

– Ability to create an affirmative emotional background while socializing with people,

– Ability to motivate decisions,
– Ability to inspire people,
– Ability to resolve a conflict,
– Ability to negotiate.

Organizing skills:

– To organize own activity;
– To take decision in common situation;
– To take a decision in irregular situation;
– Ability to behave in conditions of competition;
– Ability to share resources and assess the situation for the object in view.

Ability to deal with data:

– Forecasting the development;
– Planning the activity;
– Ability to analyse;
– To set a goal;
– To generate new ideas;
– To support stable creative advance and development.

World's practice of training specialists at the Technical Universities showed that the qualification and competitive ability of the graduates will be considerably increased, if at the period of training they master general engineering and special disciplines as in their native language as in the most popular foreign languages. In those countries where there is a high verbal environment different scientific and pedagogical Universities and traditions are developing now. Any developed high school of the country has an individual "face of higher education", that will give our students a great possibility effectively to get all necessary attainments, skills and experience.

The basic requirements for a young specialist should be formed due to the following statements:

1. Requirements to skills and experience of a specialist;
2. Requirements to personality traits of a specialist;
3. Requirements to personal culture;
4. Ecological manners.

The main requirements to skills and experience of a specialist are:

–1.Ability to analyse and make decisions;
–2.Ability to organize processes of communication;
–3.Ability to generate ideas;
–Information technology skills;
–Skills and experience in the field of foreign languages;
–Ability to organize activities;
–And so on.

Nowadays the notion "ecological culture" hasn't been formed yet. However educational specialists proper consider this category to be a rising of ecological competence, acquiring knowledge and skills of nature-oriented activity and eco-conformable behaviour. But regular acquiring ecological knowledge will not be a guide for action, if there is no wish to use them in everyday life and work activity. The investigations have shown that the level of students' knowledge has been rising steadily year after year, but the level of ecologically reasonable activity is still low.

There are system and functional criteria for the evaluation of the level of student's willingness to ecological education and training. The functional criteria include classified ecological knowledge. The system criteria include demonstration of responsible attitude to the nature, forming of personality traits.

Modern methods of training are widely used for ecological education, with using visual articles for demonstrativeness of idea of ecological atmosphere, and also complex systems of training and personal computers.

The system of social relations of any specialist is an important feature expressing ecological culture of a future specialist. It includes realization of duties concerned with ecological education and culture, as a duty to the native country. The understanding of high ethical validity of ecological requirements, first of all for a person, and also realizing necessity of working with forming ecological culture in the community and society.

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TO THE QUESTION ON THE ORGANIZATION JF PHISICAL TRAINING STUDENTS WITH THE WEAKENED HEALTH

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The illnesses got still in the childhood or during study at school, in most cases progress in student's years. The umber of the students engaged in physical training in a special medical group increases annually. So according to G.I. Bulnaeva and O.M. Bujkova (2004), the percent of practically healthy students in 1992 made 54.6 % and a decade later 42.0 % .In a given situation both the theory and practice on improvement of student's youth by means of physical training require further perfection. Besides a new approach to the development of physical training and sports carries cardinal changes in organizational structures of high schools, programs and plans which provide process of improvement, especially for people the weak health. In higher educational institutions on the faculty of Physical training the students with the weakened health are engaged in special medical groups.

The most important method of struggle against illness is a healthy way of life the component of which is an active physical training. In conditions of worsening ecology and constant stress health are marked essential deviations in a state of students'. The interrelation between physical readiness, the general condition of an organism and capacity for work which is made special demand on by manufacture (Kabachkov V.A., 2006) is getting most visible. The future experts having poor health and weak physical development, as well as chronic diseases, cannot master curricula to a considerable extent (Balsevich V.K./ 2002, Korepanova E.V., 2003, Pakulina S.A., 2004).

Carried out comparative analysis of a state of health, control test of physical development and physical ability of students of Astrakhan state technical university (ASTU) has convincingly shown, that for last years the steady tendency of downturn of a level of physical capacity deterioration in functioning of the basis organs and system, decrease in adaptation to work to be done is observed. The results of medical examination show, that the majority of applicants for enter have chronic diseases and in some cases more that one (Kuznetsov I.A., 2006).

The most actual is the problem of physical training of the students related to a special medical group by the state of their health. Moreover, there is still no scientifically proved technique of physical training for the given contingent. Some high schools practice unreasonable exempt of students from physical training that results in progressing consequences of hypodinamia and in deterioration of physical and capacity of the students. Quite often physical training of students of special exercises is applied without taking into account the functionalities and a state of their health (Taran V.A., Larin J.A., Larionova N.N., Shcherbina V.A., 2004). In this connection, it is rather important to organize physical training for them in a special way to avoid situation when impellent activity leads to the deterioration of morphohunctional conditions of an organism rather than to recovery. The individual, strictly differentiated approach to any particular student is vital for physical training when for a basis the diagnosis is taken. It has allowed distributing students ASTU with the weakened health into following:

- Cardiovascular diseases – 57 %
- System of organs of digestion – 23 %
- Organs of sight – 16 %
- Other organs and systems – 4 %

Such composition of groups in our opinion is logical as it assumes preservation of the basic pedagogical principles of physical training, takes into account individual opportunities, indications and contra-indications of application of means and trainings.

Thus, on the basis of the analysis of a health state of ASTU students it has been revealed, that every year the number of special medical group which require strictly individual physical trainings increases. Distribution of such students in to groups on the basis of the revealed somatic frustration of the various register will allow raising effectively the quality of physical training influence on the weakened

organism. Practical decisions in this field will resolve a number of the contradictions taking place in a modern education system, including those between continuous growth of requirements to students and decrease in adaptable opportunities.

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THE DEVELOPMENT OF PROFESSIONAL CULTURE OF FUTURE DESIGNERS BY STUDYING OF ALTERNATIVE TECHNIQUES AND MATERIALS IN DECORATIVE TEXTILE

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At the present time the question of synthesis of Arts is studied enough. This synthesis is expressed as relations between Architecture, Statuary art, Pictorial and Monumental Art. Such moments as, the character of interaction between Architecture and certain directions of applied decorative Art, especially the decorative textile in interior appearance, are poorly known.

At first sight it seems that using textile in design of interior is a very specific sphere of human activities. Textile is an important element that makes style, form and color elements of interior.

In the modern design the profitable aspects are alternativeness, irregularity of decisions, approaches and designer's fabrics. The unique character, in the context of designer's version makes such things unique.

The State Educational Standard of the specialty 0524.00 – "Design" includes disciplines of the course "Decorative textile". Unfortunately, there is not much attention paid to the disciplines while professional education of designers. These disciplines are excluded from the curriculum and were substituted for other subjects at some Universities.

These contradictions make us attack this problem that is the significancy and originality of the problem. The Universities must be oriented on the world tendencies in the field of new technologies and materials. Nowadays it is difficult to follow the traditional directions in design of the things. The atmosphere of experiment is unaffected. The irregularity of decisions is realized in frontal and volume and graphical fabric compositions. The volume and graphical compositions are such things as: screens, frame static and kinetic compositions, volume lamps (floor, desk, overhead, wall and embrasure;), and also frameless lamps made of bonded fiber and frame lamps of any shape, textile furniture (shelves, arm-chairs, decorative pockets and other), overhead decorative textile compositions. Panel, wall horizontal decorative compositions are frontal.

At the Orel State technical University we are trying to take into account all modern tendencies of fashion, new technologies and materials when we train designers at the chair of "Design". That's why on the first stage of decorative textile studying the students study traditional materials, test all classic methods, styles, then they experimentally find out new items of designer's finds. The alternative materials in the decorative textile are the synthetics of glass, metal, wood, stone and textile, using coloring, synthesis of different textile methods (batic - macramé, batic - tapestry, tapestry - patchwork), heating, phyto-design, buttonhole tapestry, pyrography and other methods.

Thus, studying of alternative techniques and materials in decorative textile plays great role in the development of professional culture of future designers.

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APPLICATION OF MATHEMATICAL MODELING APPROACH IN THE EXTENDED PROFESSIONAL EDUCATION

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The modern development of the system of extended professional education (EPE) is impossible without enhancement and development of practice of creation of reference and didactic materials, electronic (multimedia) textbooks as a methodical and informational support to the educational programs. Teaching in the frameworks of EPE is to be carried out with the intensive methods provided for the active work of students and to come along with recommendations on using software to solve the specific problems of each individual user. The main position in this program is taken by the IT based on the Internet with application of mathematical modeling. Preeminently due to them the relatively complex physical phenomena and processes in technical systems are being visualized.

Tomsk Polytechnic University is involved in making electronic textbooks (ET) and electronic teaching and methodic complexes (ETMC) based on the method of mathematic modeling and directed to be used in EPE. The developed program products make it possible to receive deep knowledge in a subject and they are targeted on comprehension and analysis of knowledge got during the retraining process, which is very essential for professional activity.

However, the successful use of mathematical modeling approach requires theoretical knowledge and skills to assign and accomplish an applied task arising in the specific subject area. Besides, special consideration should be given to practical work directed to acquire stable skills of working with PC.

If traditional methodological principle of teaching based on the extensive knowledge accumulation makes it possible to acquire theoretical knowledge in some measure, than this principle does not train to get the skills to assign and accomplish the applied task. ET, developed on the basis of traditional principals of didactics, mainly do not meet the requirements both of a trainee and a teacher, especially when the time consumption should be minimal and the training level – maximal.

ET and ETMC created with application of mathematic modeling approach allow eliminating a number of such shortcomings. They have the advantages over traditional technologies as deep elaboration of knowledge in fundamental disciplines of a technical higher education institute (physics, mathematics, electric engineering), interconnection between the disciplines, possibility of monitoring of the outcomes of teaching the trainees within the whole period of training, dialogue between a trainee and a teacher.

The structure of a course, based on the mathematical modeling can conditionally be divided into two constituents. The first deals with the disciplines of basic technical profile; and the second concerns a specific direction or specialty of retraining. Each of the constituents is supplied with the supplementary test material. Tests of the first constituent are directed at checking the level of knowledge and understanding of the material. In order to check the knowledge in the second constituent of the course, the testing system should be developed, which could make it possible to asses the skills on modeling the processes of complex technical systems.

While creating ET and ETMC, it is important to understand the context and sense of each particular course (discipline), which task in training a specialist it accomplishes an how to base these issues on the mathematical modeling approach. To put it differently, mathematical modeling makes it possible to perform the functions of the basis for a system approach in technical education.

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THE LEVEL OF THYROID HORMONES IN BLOOD SERUM OF PIGS IN RELATION TO THE BREEDING FOR IMPROVED PRODUCTIVITY

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Modern approaches to breeding, raising and efficient industrial maintenance of farm animals demand objective scientific methods of evaluation.

Hormones of thyroid gland produce biological affect upon most physiological functions of organism. Thyroid hormones control growth and development of animals, the rate of basal metabolism, the exchange of proteins and fats. The key hormones of thyroid gland's follicular part are thyroxin (T_4) and triiodtyronin (T_3).

The experiment was made on Precocious Meat pigs (SM-1) of Novosibirsk breeding on the experimental training farm "Tulinskoye" of Novosibirsk State Agrarian University.

The experimental animals were in control fattening. Their age was 6 months. The data was processed statistically through computer programs MS Excel 2000, Statsoft Statistica 6.

The controls in the experiment were the progenies from 6 SM-1 boars. The content of thyroid hormones (T_3, T_4) was explored as well as the amount of total protein and triglycerides in the blood serum of the pigs.

While exploring the value of thyroid hormones in the animals' blood in relation to meat productivity it was found that the concentration of thyroxin and triiodtyronin was higher in the pigs of longer carcasses.

The relation between hormone activity and productive traits of the animals was determined during the calculations of correlation coefficients. The correlation between T3 and the weight of the back third of a half-carcass was equal to 0.435 ($p<0.01$). The correlation between T_4 and fat thickness ($r = - 0.305$; $p< 0.05$) was opposite and less.

As a result of the experiment it was revealed that the progeny of the Svetly 1704 and the Soviet 1618 had the higher content of hormones in thyroid gland, the higher level of protein and the lower number of triglycerides in blood serum.

The data obtained is the evidence of higher concentrations of thyroid hormones in the blood of pigs with improved productivity traits, they activating protein synthesis and inhibiting the mobilization of fats in organism.

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SYSTEM ORIENTED MANAGEMENT OF ENVIRONMENTAL SAFETY

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Everyone as a consumer and producer faces to some ecological situations in the everyday life or work activity. He must know what he consumes and produces from a position of environmental safety. And it is impossible to obtain this result without development of ecological culture for modern specialists and training of industrial personnel. In Russia a complete discrepancy between the level of environmental culture of industrial personnel and requirements of supporting and management of ecological safety of workers was being created. This gives a possibility to consider the development of ecological culture between students of a University and industrial personnel to be a very urgent for every metropolis nowadays, especially for Togliatti city well-known for its greatly developed ecologically destructive production.

At the Togliatti State University the students of the Chair of quality control, standardization and certification and the Chair of management for industrial and ecological safety interviewed the industrial personnel at the three major plants **(300 people).** The head count showed:

– 0,7 % know what is ecology and environmental education and realize its targets;

– 97% don't know what to do in a certain common (everyday) and manufacturing situation;

– 30% of respondents consider ecology to be connected only with environmental pollution, excluding their own participation;

– 99,9% do not realize that the environmental mess rises from “a piece of paper dropped in the street”.

During the training of modern specialists at the University we worked out and adopted a test material for diagnostics of structural components of ecological culture. Herewith the level of standardization and unification of elements and the legal, aesthetic, technological, ergonomic rates of ecological culture forming among the students of the University are being observed there. The evaluation system in the projecting of technological realization of ecological culture development by an example of the University is determined with the quality of chosen control characteristics, diagnostic methods, and strategies of control testing and the processing of results. There is a necessity of concrete criteria to be controlled during the process of ecological culture development. One of such criterion is an entry level which is found by testing. To get a guaranteed result of training and to determine the level of ecological culture the new kinds of test procedures, suggested by Yu.K. Chernovaya and V.V. Schipanov, were applied. The controlled characteristics consist of the quality level of the content (the quality of information advertised, consistency, advance coefficient and the parameters of categorical direction, and the parameters of functioning (competency, overwork). All the used diagnostic methods applied for the forming of ecological culture among the students were standard, and consequently, these methods meet the case of validity, reliability and efficiency. As a valuation we used mathematical expectation offering these properties. For the factors of use it is necessary to work out a system of criteria of relation to one of the levels to interpret the findings.

The description of the measuring object lets to find out relatively categorical connections between the given measuring object and its conceptual features. To organize the system evaluation we chose the ecological competency of a specialist – as an out parameter, and the level of ecological culture development – as a controlled factor. The ecological thinking and competency are being observed by us constantly with the help of the tests. The description of the measuring object can be calculated and measured through the system of quality levels and by marking conceptual features. This exact way of the measuring object lets to find out relatively categorical connections between the given measuring object (the feature of empirical object) and its conceptual features. We set a problem to observe the process of forming of ecological culture. In order to provide the effectiveness of our diagnostics we used tests and methodic of the known authors which are widely used in the pedagogical and psychological practice. The ecological competency Y was described by the tests of V.I. Sivoglazov, T.S. Suhov and T.A. Kozlov.

The ecological culture is defined by 5 components: ecological competency Y; ability to recognize the ecological situation among all variety S; ecological thinking, ecological philosophy F; ability to use all the diversity of methods of ecology M; reflexive abilities R.

These components are divided on two groups, one of them can be measured by objective methods – these are objective rates, the other – only by subjective or expert methods – these are subjective rates. Among the objective are S and F rates. For the measure of these rates a group of 4 experts was organized. This group was to allot the mark by the five point system.

Each expert noted down the results of his estimation in a special report form. After that the results of all the experts were averaged, then divided by the maximum possible point (5), and we had got the relative parameters S and F, which were noted into the table. The competency and ability to mark the ecological situation are determined by the achievement test results as a position of the amount of the points of this test to the maximum possible. The reflexive abilities as a complex formation, including some components (reflexive thesaurus, evaluative abilities, readiness to the self-evolution), are measured on the basis of the known reliable and valid methods. The received differentiated rates of the reflexive abilities based on the additive pooling (summing) made R. The data of the table was objected to a statistical analysis. Here all the data in each column were examined for the correspondence to the normal probability law, the average rate of dispersion parameters was here

also determined and the integrative rate of ecological culture of the convolution of Y, S, F, M, R by the formula:

Ecological culture (EC) = 1/5 (Y+ S+ F+ M+ R), (1)

The average rate (number) for all the class of the population is calculated by the formula:

$EC_{average}=1/5 (Y_{av}+ S_{av}+ F_{av}+ M_{av}+ R_{av})$, (2)

The root-mean-square deviation σ and the estimation through ECav are used for the plotting of the tolerance interval of the ecologiacal cultures:

$(EC_{av} -2 \sigma\sqrt{n} , EC_{av} +2 \sigma\sqrt{n})$, (3)

where n – is an amount of the respondents.

In this formula a coefficient 2 preceding a fraction $\sigma/\sqrt{n}$ is a real approximate value of Student's test, when the confidence level a=0,05 and the amount of people that defines the amount of the number of degrees of freedom distribution.

The necessary and sufficient conditions for the development of the ecological culture of a student are:

a) the orientation towards the awareness of the notion „the environmental quality" in the daily activities that suposses an exceeding the bounds of the adopted techno stereotypes;

b) the development of the ecological culture based on the suggested measures;

c) the forming of motivation and ability to use concrete ecological situations for the development of the practical work of the production industry.

The worked out technology of the ecological culture forming is meant for the mentality establishing of a person, in the context of the educational approach. To ogranize the complex of contrlol actions we marked the most important factors and the permissible limits of their variation for stability. We also examined the projecting of the controlled parameters based on a mathematical model, where the system connections between the mechanisms of projecting, functioning and quality control on the basis of the offline methods. For the estimation of the process of ecological culture development we suggested the method of evaluation of its forming.

The foregoing allows to say that the system-oriented control under the ecological safety and favour to an understanding of priority of the ecological thinking and the philosophy of the ecological culture in all the occurent situation, that confirms the statements of the suggested hypothesis. During the organized research the main scientific results and some directions of the following working of this problem were defined. The main features of the ecological culture is considered to be a conceptual and activity thesaurus, ability to mark the ecological situation from all the variety of situations in the environment, herewith using the special methods and means, reflexive abilities. Because for a human of the future, these components put in the mind the psychological inconsistency of production management with 'don't care' attitude to the facts of misuse of the environment in all the agricultural spheres.

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THE BASIC THEORETICAL ASPECTS OF NEW CONCEPT REALIZATION OF RIGHTS AND FREEDOM OF THE PERSON AND THE CITIZEN IN RUSSIA (BY THE EXAMPLE OF REPUBLIC BASHKORTOSTAN)

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The given scientific article is devoted to research of an actual problem for Russian Federation showing the new concept of the rights and freedom of the person and the citizen. The authors of the article examine the basic theoretical aspects of realization of new concept of person's and citizen's rights and freedom in Russia in the view of realization of the given concept in Republic Bashkortostan as one of subjects of the Russian Federation.

The person in the system of the right, the legal person is, first of all, the subject, the carrier of certain actions. In the concept of Russian philosopher of right (the beginning of XX century) N.Alekseev, the subject was allocated a role of " the deepest element of legal structure" (See: Alekseev N.N. The basic of philosophy of right. Prague, 1924.-C. 76). E.Pashukanis defines the person as the subject of the right - "as an atom of legal theory, the elementary, further an indecomposable element" (See: Pashukanis E.B. Selected works on general theory of the right and the state. - M., 1980.-C.102). Russian philosopher I.A.Iljin distinguished, that "right regulations are based upon mutual recognition of people" (See: Iljin. About essence of sense of justice // volume 2. - M., 1993. – 256 p.). **P.Riceur** defines concept of the subject of the right as follows: "The subject of the right is anyone. I am anyone to the attitude to all. We enter into legal space when we consider ourselves as "anyone" of all other "anyothers" (See: **Riceur P.** Triumph of language above violence. Hermeneutic approach to philosophy of the right // Questions of philosophy. - 1996. - №. 4, 30 p.). Russian philosopher B.P.Vysheslavtsev writes: "Ideal of the right is a free subject, homo sui iuiris, the independent person, which itself argues, itself estimates, itself chooses the direction of actions » (See: Vysheslavtsev B.P. Crisis of industrial culture. Marxism: Neo-socialism. Neo-liberalism. - New York, 1953, 229 p.).

Hence, the legal subject is a person, being as unity of the attitude to another (to anyothers) has the direct attitude to the right, to realization of the rights and freedom of the person and the citizen. But the real personal freedom becomes possible in the society of genuine democracy. Transition to such society is historically long process which is connected to formation of a civil society. The category "civil society" reflects a new qualitative status of society which, first of all, is based on the advanced forms of its self-organizing, self-control, in an optimum combination of state, public, individual and personal interests. Freedom and human rights, his private interests should be considered not from the position of "economic person" for whom freedom is the property, but differently. Further it is necessary to define precisely, that the personal freedom and a legal status of the citizen does not mean identity. Freedom possesses normative.

Therefore, the person finds freedom as a result of the ability to submit to its normative requirements. Externally the form of person's life freedom are the social norms determining the measure, allowable borders of freedom. It is not only legal norms, but also traditions, customs, moral, religious norms. Laws, if they have legal character, are, by words of K. Marx "the Bible of freedom". The main legal means of fastening, recognition of personal freedom by the state is the Constitution. Basic novelty of the Constitution of Russian Federation in 1993 is the fact that the personal right has never been a practical state priority in our domestic history before.

The initial principles of the constitutional status of the person are:

1) personal freedoms; 2) belonging to the person of fundamental laws and freedom from birth and not their estrangement; 3) conformity of the status of the person in Russian State to requirements and the standards developed in the world community; 4) a combination of individual interests of the person to interests of other persons, societies, states; 5) universality of fundamental laws, freedom and duties; 6) legal equality, that is equality of citizens, including equality of all before the law and court; equal rights and freedom for men and women; 7) Direct action of the rights and freedom of the person and the citizen, conformity to the constitutional bases of the status of the person of his fastening in the current legislation and practical realization; 8) guarantee for constitutional status of the person, his rights and freedom. (Constitution of Russian Federation. (1993) - an items 2, 6 part 2, 15, 4, 17, 18, 19, 55, 64; Avakyan S.A. Constitutional Law of Russia. M.: the Moscow State University, 1996., 34 p.).

The sense of the new concept of the rights and freedom of the person and the citizen is that the person began to be considered first of all as the person with his interests and rights, instead of "screw" of state machinery, the person is proclaimed as the supreme value. If to address to the retrospective analysis it is necessary to note that there were three concepts of the rights and freedom of the person in Russia (USSR) which were typical for three historical periods: 1917 - the middle of 30th; the middle of 30th - the end of 80th; the end of 80th - present time. The feature of after revolution concepts of the rights and freedom of the person is the class approach. The class approach of 1917-1936 was replaced with civil in 30 - the end of 80th. Difference of modern concept (the end of 80th - our days) from the concept of 30 - 80th is the following: the Person is declared as the value (the state exists in the name of the person, instead of the person for the state); The person is considered as the person with the ideas, problems, interests and then as the subject of the state; Interests of the state and the person should be harmoniously interconnected, instead of suppressing each another; Human rights are inalienable

and belong to him from a birth but not granted by the state; the Constitution adjusts only fundamental laws and freedom of the person while the number of them is much more, than listed in the Basic Law; Human rights can be limited only by the federal law strictly specified in the Constitution.

Legislative registration of system of human rights concerns to number of the basic characteristics of development of society and acts as one of manifestation of institualization of its more general characteristic – humanization of social and law attitudes. Presently the idea of humanization has found reflection in a number of international documents where Russia takes its part.

First of all it is General declaration of human rights (1948), International pact about the economic, social and cultural rights (1966). (See: Kartashkin V.A., Lukasheva E.A. International acts about human rights: the Collection of documents. M., 2002. - 44 p.). The ideas of humanization of social and legal relations find their place in modern Russian legislation. Leadership of the law is the Constitution of Russian Federation which proclaims, that the person, his rights and freedom are the supreme value; recognition of observance and protection of the rights and freedom of the citizen to be the first duty of the states (item 2). The axiological aspect of constitutionalism of Russian Federation is defined by its ability to satisfy the corresponding purposes (for example: the creation of the conditions providing a worthy life and free development of the person (item 1, chapter 7 of the Constitution of Russian Federation) one of characteristic manifestation of humanization of societies is recognition of human rights for the non-property blessings, that in particular is reflected in the legislation of Russia.

In scientific researches and development of the legislation addressed to the rights and freedoms of the person a special place is devoted to the following: the right to individualization of the person, protection of honour, dignity, business reputation; the right providing the inviolability of person, corporal

inviolability, protection of life and health; the right to inviolability and secret of private life. The following works were devoted to these problems: S.A. Aleksandrov, B.T. Bezlepkin, A.B. Belyavsky, A.M. Beljakova, A.G. Berezhnov, Z.S. Gladuv, V.V. Gljantsev, S.E. London, N.S. Malein, M.N. Maleina, M.F. Malikov, M.G. Stojakin, V.L. Suhoverov, I.E. Farber, E.P. Chernovol, N.A. Shajkenov, A.E. Sherstobitov, M.J. Shiminova, K.B. Jaroshenko.

In January, 2005 the State Assembly (Kurultai) - Republics of Bashkortostan, in connection with expiry of the term of powers of former Representative, the second Representative of Republic Bashkortostan on human rights was appointed. The tasks facing to the first Representative of Republic of Bashkortostan on human rights for realization of law protection institute of the republic basically have been successfully fulfilled. Keeping continuity on the basic directions of activity in the conditions of dynamically developing Russian and republican socially - political and legal system, the Representative of Republic of Bashkortostan on human rights should lift efficiency of the constitutional institute of protection of the rights of citizens on qualitatively new level.

Scientists - jurists developing the general-theoretical problems anyhow connected to selected subject of research: V.M. Baranov, B.T. Bezlepkin, A.V. Belyavsky, A.G. Berezhnov, V.V. Glyantsev, M.F. Malikov, N.S. Malein, M.N. Maleina, F.M. Rudinsky and many others. Still the given problem remains not to be resolved.

In essence, the Representative of Republic of Bashkortostan on human rights is called to be the arbitrator between authority and society. The Representative's independence from any state bodies and officials, the principle of non-interference to his work is an indispensable condition of his effective law protection activity, the guarantee of objectivity and impartiality.

The Representative's effective work is impossible if separated from all event both in Republic and outside without detailed studying an operational experience of regional and foreign representatives of law protection institute of Europe.

With the beginning of work of newly appointed Representative of Republic of Bashkortostan on human rights the structure of Advisory is expanded up to 12 persons. Under the recommendation of the heads the highly skilled lawyers of corresponding departments specializing in various areas of the right have been included in structure of Advisory council. At the sessions conducted by the Representative, members of Advisory council accepted active participation, stated critical remarks, made offers on discussed questions.

The carried out work of the Representative of Republic of Bashkortostan on human rights and his services on consideration of citizens' appeals, interaction with authorities of all levels and law-enforcement departments, the analysis of official analytical documents, information of mass-media allow to draw a conclusion that in 2005 in Republic of Bashkortostan as a whole all interested parties carried out purposeful work on the further expansion of conditions for realization of constitutional laws of citizens, the further dynamical development of economic potential of republic, political institutes first of all is provided, the preparatory stage to transition to local self-management is completed.

The constitution of Russian Federation puts the right to life, health, honour and advantage in a rank of the natural and inalienable rights of the person that assumes effective protection and protection of these rights. Providing the most fair and effective restoration of the broken right and compensation of caused harm is the main task of judicial authority.

The international community has developed not only universal standards of human rights, but also the mechanism of legal protection of the given rights and freedom.

Protection of the rights and freedom at the international level carry out: the United Nations Organization (corresponding committees); European Court on Human Rights; other establishments.

The given rights are protected in Russian Federation by: constitutional-judicial bodies (the Constitutional Court of Russian Federation); judicial bodies (Courts of General Jurisdiction); enforcement authorities (administratively); diplomatic, consular

establishments abroad; by lawful self-defense of person's rights.

Thus modern conditions in Russia as in a lawful state, protection of human rights and the citizen obviously becomes more and more one of bases of public progress which includes universal interest, a priority of universal values. The true progress is impossible without certain providing of the rights and freedom of the person, including the right to honour, dignity and business reputation (See: Shergeng N.A., Egorov N.P. Moral harm: social - legal aspect of concept. - Ufa: Bashkortostan State University, 2005. - 208 p.).

Materials of the Conferences

MATHEMATICAL MODELLING OF MANAGEMENT IN MULTILEVEL SYSTEM OF PUBLIC HEALTH SERVICE

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The general task of public health service management as a whole, as well as treatment-and-prophylactic establishment management of public health service based on information technologies assumes, first of all, the development and application of some "tool" of management which is the mathematical models describing the process of organization functioning. In other words, in «the virtual environment», formed by information technologies, mathematical models act in the role of some «matter» on the basis of which the analysis and synthesis of managing influences is carried out.

In modern conditions, while developing mathematical models principles of systems approach are widely used, the basic among which are the following:

principle of unity: joint consideration of system as the whole and as sets of elements from the position of realization of general aim;

principle of connectivity: as a rule the approach is quantitative for any part together with its connections with environment;

structural description of system constructed for majority of cases by hierarchical principle.

Mathematical models of optimal control of public health service should realize the principles of system approach taking into account specific features of public health service. In 1982 E.N.Shigan stated the methodology of systems approach, classification of methods of system researches is made in the field of medicine in the work «Systems analysis in public health service» [1.2]. In this work the conceptual device of systems analysis and its place in managerial process by system of rendering of medical aid is considered.

1. System of public health services is the complex self-organizing system which elements are people and technical objects. The specific feature of such systems is the presence of theirs own purposes not always conterminous to the global purpose. The self-organizing systems possess the following attributes: stochasticity of behaviour, not stationarity of separate parameters and processes. There are also such attributes as unpredictability of behaviour, ability to adapt to changing conditions of environment, to change structure during interaction of system with environment, preserving property of integrity, ability to form probable variants of behaviour and to choose the best from them. System of public health services is complex organizational system. As rule the organizational systems are based on hierarchical principle: the subordination of lower levels to upper levels.

The account of own purposes of elements does not only brings an uncertain factor in process of its functioning, but demands studying and modeling both the system as a whole and its separate elements (subsystems).

The system includes set of the interconnected subsystems which functioning is multi-purpose, directed on achievement of several own purposes.

2. The system is dynamic, and its condition is defined by big enough set of quantitative indexes.

3. The system has set of uncertainty factors and accidents and it provides necessity of use of stochastic models.

The listed attributes allow to relate system of public health services from the point of view of mathematical modeling to complex control systems which can be submitted by three-level model (fig. 1).

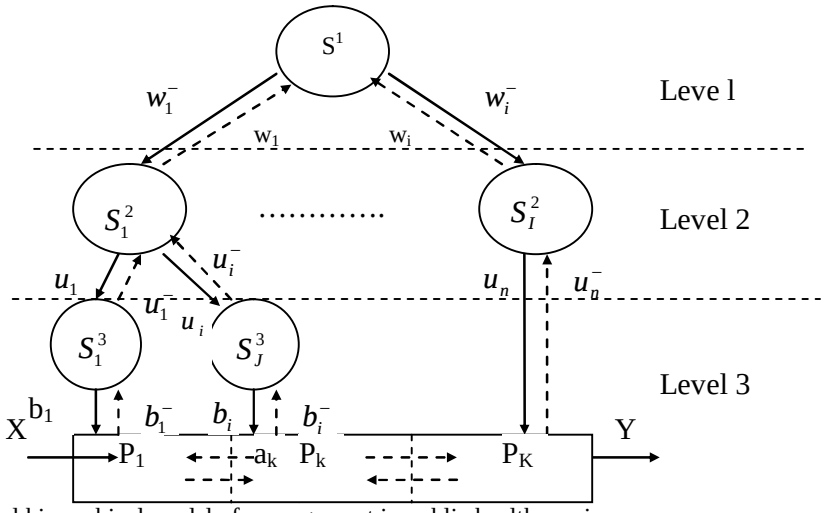

Fig. 1. Three-level hierarchical model of management in public health service

If to consider the system of public health services as a whole, the top level of management S^1 is the Ministry of Health of the Russian Federation. The level $S_i^2, \quad i=\overline{1,I}$ is submitted by bodies of territorial management of public health service. The level $S_j^3, \quad j=\overline{1,J}$ is a level of medical establishment. $P_k, k=\overline{1,K}$ represents object of management which is submitted by the state of health of the population. It is the level of birth rate, diseases and death rates, medical-ecological and medical-climatic parameters, etc.

If we consider such complex systems of public health service as polyclinics, hospitals, clinics, dispensary, cardiological and other services, the top level of management S^1 is the Head Health Service (the head physician), the level $S_i^2, \quad i=\overline{1,I}$ is submitted by branches, the level $S_j^3, \quad j=\overline{1,J}$ is the level of the doctor (the doctor of the general practice or the particular expert). As object of management $P_k, k=\overline{1,K}$ is the state of health of the population.

As complex system of public health services it is also possible to consider processes: medical-diagnostic, preventive, dispensary, educational, etc. Interpretation of levels of management in this case will be another.

There are also other elements of control system of public health services to which it is possible to relate system of obligatory medical insurance, system of voluntary medical insurance, medical associations, associations and the unions of consumers, etc.

The development of complex systems causes the problems concerning not only to properties of elements making them and subsystems, but also to laws of functioning of system as a whole. So it results specific tasks:

definition of the general system structure;

organization of interaction between elements and subsystems;

account of influence of an environment;

choice of optimum modes of functioning of system;

optimum control of system, including optimum decision-making at all levels.

In complex control systems, according to [3] the following concepts of management are possible:

authoritative (command) when orders, instructions of higher body of management should be carried out strictly by all subordinate objects, i.e. it is supposed that the higher body in all situations operates rationally (optimum);

democratic (conciliatory) when higher body, before issuing the order, previously will coordinate, i.e. discusses with subordinate objects;

scientifically grounded when research activities are previously carried out,

mathematical modeling and calculations with the real data and only then (after the coordination at all levels) is issued the corresponding order;

mixed when the democratic concept is applied on one sections, on another - authoritative, and on the third sections – scientifically grounded.

It is clear that in a real life rational management of complex system can be carried out only applying the mixed concept at a rational combination of authoritative, demographic and scientifically-grounded, proceeding from economic social and ecological criteria.

The scientific substantiation of all accepted decisions now demands both too great volumes working hours, and material and financial assets. As, on the one hand, the level of development of science in the field of management of complex systems at the given stage does not correspond to advanced achievements in the field of a computerization, and on another - the administrative personnel accepting and supervising execution of decisions, not always having corresponding scientific preparation.

The democratic coordination of all accepted decisions without a sufficient scientific substantiation also demands a lot of time for discussion and the coordination (though less), but thus accepted decisions will be less concrete, that will lead to inevitable losses at their realization.

The cheapest is realization of the authoritative concept when it is not required to waste time on the coordination and discussion of decisions. It is necessary to bring them to executors only. However, if the higher body of management is badly equipped technically, completed with experts with low qualification and a small operational experience in a control system, acceptance of erroneous decisions resulting in large material, ecological and social losses is possible.

Significant difficulties in management of complex system of public health service arise also in connection with multilevel hierarchical character of objects (subsystems) and criteria of their optimization. Basically it occurs because of weak methods of decision making in multilevel hierarchical systems in conditions of uncertainty.

These systems are characterized not only by big number of elements and complex structure, but also by more high level of the organization. A high degree of the organization of such systems, with the presence of hierarchical structure corresponds also the greater densities of the expenses connected with processing of information (non-material) streams, providing purposeful behavior of dynamic system that causes wide draft on funds of computer facilities and formal methods of decision making while managing such systems.

When deciding optimized tasks in management of complex systems of public health service it is necessary to apply vector criteria which allow to take into account optimum technological modes of separate objects. At the same time the chosen optimum mode should provide achievement of ultimate goal of subsystem of public health services. It is to maximize quality of rendering medical aid. For this purpose it is necessary to carry out the control and management of one of the major processes, influencing on an eventual result – the process of rendering primary medical aid.

While controlling the process of rendering medical aid various parameters are used. They characterize this process only indirectly, frequently they are inconsistent and usually developed for concrete medical establishment or territory. Therefore it is necessary on the basis of lines of models and algorithms, on the various parameters received on the basis of information technologies to coordinate decisions for various levels of system and inside it. Thus it is required to make decision at presence of complex multilevel hierarchical system of models of management in public health service.

Thus for tasks of the control and management it is necessary to create a uniform method of making decision in multilevel hierarchical systems in conditions of various kinds of uncertainty.

Hierarchical management structure has been caused by the escalating complexity of technology of controlled objects creating big difficulties for a centralized direction. There was necessity of division of all decision-making

process for such number of levels so that the task solution of optimization for each of them was not complex. But with occurrence of multilevel hierarchical control systems the new task of coordination of decisions accepted in all levels of management has appeared also.

The general scheme of coordination in two-level system is reduced to the following. The elements transfer a set of variants of the work in the center. Each variant represents the vector parameter of an element allowable from the point of view of its local restrictions. On the basis of variants received from elements the center forms the plan, optimum from the point of view of all system [3]. This plan is transferred by elements and further is detailed by them.

To advantages of hierarchical structure of automated management in which at the bottom level there is a plenty of simple tasks, and at higher levels - a small number of challenges, it is necessary to relate (according to the foreign data) decrease in a total cost of information handling in system, increase of throughput in networks of the computer and stability to refusals. Critical functions for system should be carried out by local control systems at failure of a server or communication lines.

Now a big attention is paid to the questions of making decision in complex organizational hierarchical systems both in our country and abroad. The feature of these tasks is the absence of material flows between various levels of hierarchical system.

The basic points of the theory multilevel hierarchical systems have been developed by M.Mesarovich and his cooperators [4]. In this work for the first time the essence and interrelation of three basic categories of hierarchy is opened: stratification, multisection and multiechelonment.

M.Mesarovich defines three types of hierarchical systems which somewhat reflect classification of hierarchies. He enters three concepts of levels:

1. Level of the description, or abstraction;
2. Level of complexity of the accepted decision;
3. Organizational level.

However all three concepts can simultaneously be used in the description of real hierarchical systems

Levels of the description or abstraction. The complex system cannot be described fully and in details it follows from the definition of such system. The basic dilemma is to find the compromise between simplicity of the description that is one of preconditions of understanding and necessity of the account numerous behavioral (type of input - output) characteristics of complex system. The decision of this dilemma is searched in the hierarchical description.

The system is set by family of models, each describes behavior of system from the point of view of various levels of abstraction. For each level there is a number of prominent features and variables, laws and principles to describe the behavior of system. To make such hierarchical description effective, in opinion of M.Mesarovich, it is necessary to reach independence of models for various levels of system.

However the assumption of full independence of strata would be unjustified, therefore the neglect of their interdependence can lead only to incomplete understanding of behavior of system as a whole.

Levels of complexity of the accepted decision. Other concept of hierarchy concerns to processes of acceptance of complex decisions. In this case family of problems is defined which try to be resolved in the consecutive way in the sense that the decision of any problem from this sequence defines and fixes any parameters in the following problem, so last becomes completely determined and it is possible to start its decision. The decision of the initial problem is reached as soon as all sub-problems will be solved. M.Mesarovich calls such hierarchy of layers decision-making.

The so-called functional hierarchy of decision-making or management concerns also to the same category. This hierarchy arises naturally in connection with three basic aspects of the problem of decision making under uncertainty: a) a choice of strategy which should be used during the decision; b) reduction or elimination of uncertainty; c) search of

preferable or allowable way of the actions satisfying set restrictions.

The functional hierarchy consists of three layers.

1. The layer of a choice: the task of this layer is a choice of way of actions. The element accepting the decision on this layer receives external data (information) and applying this or that algorithm determined on the top layers, finds the necessary way of actions.

2. The layer of training or adaptation. The task of this layer is a concrete definition and narrowing of set uncertainties with which the layer of a choice deals.

3. The layer of self-organizing. This layer must choose structure, functions and the strategy used on underlaying layers so that whenever possible it will come nearer to the global purpose. If the overall aim is not reached this layer can change functions on the first layer or strategy of training on the second layer in case of insufficiency of estimation of uncertainty.

Organizational hierarchies. This category of hierarchy means that:

1. The system will consist of family of cooperating subsystems;

2. Some of subsystems are decisive elements;

3. Accepting decisions elements settle down hierarchically in the sense that some of them are under the influence or coped by other decisive elements.

Though the top level elements cause purposeful activity of elements of the bottom levels, but not completely operate it. Some freedom in a choice of their own decisions should be given to elements of the bottom levels accepting decision.

Such systems are named multiechelon. The presence of some supreme command element is considered to be the basic distinctive feature of such systems; the problem of decision-making in the order this element is the basic problem in theory of multilevel systems.

Each of the entered concepts has the scope, namely: the concept of strata is entered for the purposes of modeling, the concept of layers - for vertical decomposition of a solved problem on sub-problems; the concept of echelons concerns interdependence between elements of decision-making forming system.

Despite of distinction of the specified categories, there are also the general for all three concepts of feature.

1. The element of the top level deals with larger subsystems or with wider aspects of behavior of system as a whole.

2. The period of decision-making for elements of a higher level is more than for elements of the bottom levels.

3. The element of the top level deals with slower aspects of behavior of all system.

4. Descriptions and problems at the top levels are structured, contain more uncertainties and are more difficult for quantitative formalization.

While accepting the operative decisions in complex hierarchical system the basic purpose is finding a vector of decisions $x_i^0(t)$ in each level $i, i=\overline{1,I}$ which provide a maximum of system criterion function $F(x_1^0,...,x_N^0)$ at the coordination task $x_{N+1}^0(t)$ received from (N+1) of a level of management. And decision-making process is carried out discretely in points of time $t=\overline{1,T}$ and generally, the step of digitization on management grows from the bottom levels to the top. The part of decisions (basically at the bottom levels) is characterized by managing influences, and the most part only coordinates work of subsystems of different levels. The assignment to subordinate subsystems of criterion functions is also the means of coordination, however in the given task it is supposed that they are already chosen.

The found decision $\{x_i^0\}, \quad i=\overline{1,N}$, should belong to the subset of modes allowable for system (technological, economic, etc.) $C \subset X$ i.e. to be coordinated with opportunities of technology.

The attempt of direct use of uniform global criterion of the top level $F(\bar{x}_N)$ with its subsequent decomposition for subsystems of all levels makes the task of optimization to be extremely complex and ignores presence of own criterion functions at active subsystems.

Besides, global criterion function $F(\bar{x}_N)$ does not depend obviously on the decisions accepted by subsystems of subordinate levels that complicates a choice of operating modes of subsystems and ways of its improvement. We shall assume therefore, that for each subsystems of first level are set the purposes $F(\bar{x}_{ij})$ on sets of decisions of subsystems, and system criterion function $F(\bar{x}_1,...,\bar{x}_N)$ depends both on global criterion $F(\bar{x}_N)$ and from criterion functions of subsystems $F(\bar{x}_N)$.

Now it is accepted to investigate questions of optimization for two-level system and to accept this task as the basic module for anyone N-level systems [6], and for a task solution on (i-1) level it is considered set result of optimization in the order i. Or if to write down $\bar{x}_N$ as:

$$\bar{x}_N = \{\bar{x}_{ij}\}, i = \overline{1,N}, \quad j = \overline{1,M},$$

where $M = m_i$ is the number of subsystems on i level of management it is supposed, that at a presence of decisions $x_{(i-1)j}, \quad j = \overline{1,m}_{i-1}$ all decisions $\bar{x}_{ij}^0, \quad j = \overline{1,m}_j$ are already accepted.

Therefore the various methods of iterative aggregation intended for iterative coordination of subtasks which parameters given with a different level of detail are used for optimization in multilevel organizational systems [7,8].

In general view the task of management in public health service can be formulated by processes as follows: to find optimum managing influences (strategy) for the complex dynamic process, providing satisfaction of requirements of a final vector of quality (standard) at limited material and a manpower.

Mathematically the task of optimum control in health service can be expressed as follows:

to find dependence $U_n^*(t)$ for stochastic criterion function $Y_k\left[U_n^*(t), \overline{A_s}\right]$

At restrictions:

$$\begin{cases} T \le T_{np} \\ \overline{A}_S \le \overline{A}_{np} \end{cases} \quad (4)$$

Where T is the term of treatment dependent on controlled factors;

$T_{пр}$ is a critical time;

$\overline{A}_S$ is vector of estimated expenditure;

$\overline{A}_{np}$ is vector of limiting expenses for treatment.

The given formulation has the general view and does not take into account the features of system described above: hierarchy, structure, activity, character of probable between elements, etc. All listed above features will be expedient for taking into account at statement and the decision of concrete individual tasks.

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VICTIMIZATION FACTORS OF THE SMALL BUSINESS ENTREPRENEURS

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The bribe-takers must tremble,
If they have stolen as much
As only they need.
When they have taken enough to share with the others
They have nothing to fear…

Criminal aphorism

The author of this article devoted 10 years to studies of problems in small business. Being a lecturer he is investigating the matter of these problems. It is possible to say the initial sociological data is objective; the results are representational, because the businessmen trust his colleague and give the objective information.

The forming of market relations lay down principally new demands to the business class. In Russia the experience of creation of new market relations has shown that the birth of a new class in the economy is rather a difficult process and it cannot depend only on the conditions.

There are many obstacles to the development of every business: small, medium and big. The analysis has shown it depends not only on the business laws, but also the range of factors not dependant on the businessmen.

In Siberia the small business sphere does not governs on the labour market, but it plays the great role in slowing down the unemployment nowadays. At the moment the industrials suppose the small business development to be paid a special, but not enough and not goal-oriented attention. That can explain the minority of the enterprise owners and the small business employees.

There are lots of reasons of such slow development in the small business in Siberia. Small business is very attackable now; it has serious problems, everyday difficulties, various obstacles and executive barriers. The favourable conditions for the small business have just begun to be created but the problems are being solved very slowly.

This research was organized in 5 Siberian Regions in the period from 2000 till 2004. The sample was formed by 500 small business enterprises; 100 respondents in 5 districts of the Region. The method of the research was an enquiry, questionnaire in writing (intramural, extramural and postal), and verbal interviewing (at business meetings, phone interview). The study purpose is to find out victimization factors of the small business entrepreneurs in the concrete Region of Russia.

91% businessmen (455 respondents) consider bureaucracy and bribery to be the weightiest factor of destabilization in the sphere of small business.

The main factor of victimization is classified by periodicity as the following:

1. Normative acts, which can be differently and unlawfully interpreted;
2. Corrupt practice at the top echelons of power;
3. Illegal revisal of control organizations;
4. Bureaucracy and red-tapery while execution of documents;
5. Assign authorization of enterprises by the overhead organizations;
6. Tax inspection by an anonymous call;
7. Front organizations of the criminals or police;
8. Financial risks;
9. Price discrimination;
10. Kickbacks;
11. Racket;
12. Wrapped financial insolvency of prospective clients;
13. Official hiding of necessary information about suppliers and demanders;

14. Letters of the regional administration about voluntary welfare work and compulsive pay increase for the employees;
15. Low employee qualification;
16. Selling of information by the employees to business rivals;
17. Unfair competitive practices;
18. Heavy costs for brass check;
19. Electronic spying;
20. Employment for getting information and so on.

Among the organizations, where entrepreneurs had to pay off rather often, are:

1. Government executive bodies;
2. Tax administration;
3. Police;
4. State Inspectorate For Traffic Security;
5. Customs;
6. Prosecutor's office;
7. Courts of law and Arbitration court;
8. Authorization system;
9. Justice;
10. Russian agency responsible for registration of property;
11. Center of Standardization ;
12. Lending agencies;
13. Consumers Union;
14. Fire Department;
15. Various business centers.

The annual President's Letter to the Federal assembly dated 1997 said: "The crime in the economy, corruption and abuse of power are going hand in hand." This statement is greatly typical for today. It is necessary to mark that the jobbery has been happening since the daytime of private industry, and, as our respondents suppose, such events become more and more usual.

In 2002 the Social Fund called "Information technologies for Democracy" (INDEM) in association with an American company «Transparency International» declared the results of the survey organized in 40 Regions of Russia. The purpose of the survey was to find out the real situation of corruption in the country and the attitude of the population to this fact. As the survey showed, among the Siberian Regions the leader in the group of the middle bribery is the Kemerovo region. This middle bribe given by the entrepreneurs to the officials was 142 thousand rubles. The Kuzbass placed itself on record by the annual sum of the bribe. It is 18 085 bln rubles that are 4 bln more than the revenue side of the Regional Budget. These results were being widely discussed at one of the seminars of "The Regional Club for Journalism" in Moscow. The spokesman was Professor Mark Levin.

On the instructions of Kemerovo governor A. Tuleev the administration of the city have reviewed the influence of executive barriers on the terms of small and middle business development in Kuzbass. They have found the following fact: the entrepreneurs pay from 2500 till 52000 rubles for the time of waiting for drawing up the documents while registration of enterprises, receipt of a license and other documents which are necessary for the entrance to the market. This period takes from 114 till 301 days. The sum of unplanned payment depends on the activity of a first-time entrepreneur, the place of business running and other factors.

The particular results of this sociological review were compared with the results of the INDEM survey. So, more than 60% of Russian people consider corruption to be the problem that endangers the safety of the country. In the Siberia Region this rate is 57% among the entrepreneurs. 70 per cent of the respondents think that Russia can be classed among the corrupted countries. 79 % of the Siberian entrepreneurs answered this question in the affirmative.

The further attempt was purposed in order to find out which of the government department is a leader at the market. The INDEM survey lightens the following statistics through Russia: executive branch of the government -98,7 %; legislative body 0,17; judicial authority – 0,86%.

In the Siberia Region the survey has the following results in rank order: the executive body (96,3%), the judicial body (63,8%), the fourth estate or mass media (58,6%) and the legislative body (0%). So called fourth estate (mass media) was written in a form according to the answers of the respondents, and was not mentioned in the INDEM survey.

The respondents said about the judicial body: "Our questions are trivial, only big and middle businessmen can give bribes to the

deputies", "We can not do the same because there is lots of money there on the top, and there is no such sums in the small business." All respondents think it is possible to give bribes to a deputy but it makes no sense.

In this research the author basically used the classification of bribes as one of corruption forms, worked out by an American Professor V.M. Reisman, because it is widely used in the world (in the USA, Egypt, the Republic Cuba, China, Kenya, Pakistan, Venezuela, Nigeria and others). This classification is used for studying bribery among the officials. The author tried to study this fact using the concrete method.

The respondents were suggested to answer the question: "If you ever gave a bribe to an official, what was the purpose?" And then the variants of answer were given:

A. Business bribe;
B. Dilatory bribe;
C. Bribery of officials.

The analyses of the answers showed that the lowest percentage among the bribery is a bribery of officials (6,98%). The entrepreneurs refer this situation to the fact that there is no possibility to bribe everyone who can influence your business. They spend money only on "an inside man" in the Tax administration. Business bribe (50,62%) and dilatory one (57,32%) are the main kinds in the field of the small business. The difference between them is only 6,7%. But they are impermanent and occasional and that is why they are used more often.

After 5 year research of this problem in the region it may be concluded that the corruption is first of all under the influence of political events.

Example 1: Our regular research was organized in the formation period of authority and administration of the Altai Region governor Mr. Evdokimov. He was a popular representative, and the entrepreneurs had great expectations about the political house-cleaning in the regional official bodies. These hopes influenced statistics: the executive body – 70%, the legislative power – 0%; the judicial authority – 12%, otherwise, the fourth estate is still on the same position -32%.

Example 2: The tragic death of the governor of the Krasnoyarsk Region, Mr. Lebed also greatly influenced on the results of the survey. The entrepreneurs were afraid of a complete outrage and supposed the executive body to be very corrupted (100%), the rating value of corruption in the judicial body increased from 17% up to 21%, and in mass media – to 36%.

As the INDEM sociologists have concluded that it is necessary to mark the small businessmen are going with the authority and corruption more strictly. In Siberia the Kuzbass businessmen had the lowest level of confidence to the Federal Government. Among 40 responded Regions the Kemerovo Region is on the 30th position, The Novosibirsk Region - the 28th position, The Tomsk Region – the 25th. The Altai Region is on the 17th position in this rate, the Krasnoyarsk Region – the 15th position.

This survey has made an effort to study the confidence and non-confidence to the Regional executive body. The analysis of the primary sociological facts is practically the same according to the INDEM information. The same results were found in the 2 polar positions: "confidence and non-confidence" were conformed by the Altai Region and the Novosibirsk Region.

The research was meant to find out real potential for struggle against corruption in the Siberia Region. The questionnaire included the following question: "Would you take part in the struggle against corruption?" And the answers were given below:

1. Yes, I would;
2. Not yet, I'd better wait what would happen;
3. No, I would not because I do not believe in positive outcome of proceedings.

The results of the All-Russian survey contain the following statistics: 30% of the entrepreneurs would take part in the struggle, 30% - would not do that because they don't believe, 40% of the respondents prefer to wait what would happen after the actions of those who prefer to struggle.

In the Siberia Region only 4% of businessmen (21 respondents) would try to protect their interests by coming into confrontation with the officials. 76% of businessmen do not believe in justness, they are afraid of possible revenge of the officials, random check-outs, which usually lead to numerous financial charges. 20% just hold

hand; they don not want run risk. The conclusion now can be expressed by the words of one of respondents, who said: "The struggle against bureaucracy on the top is the same as the struggle against the windmills".

The greatest non-confidence was expressed by the entrepreneurs in the Kemerovo and Novosibirsk Regions. The percentage of such businessmen is properly 92 and 89. One of the businessmen expressed his attitude to this situation by an old philosophic wisdom: "Laws are like net: it entangles the weak one, but the strong can tear it."

There is rather low level of pessimistic mood among the entrepreneurs in the Krasnoyarsk, Altai and Tomsk Regions. The highest percentage of optimists is in the Tomsk Region (47%) and the middle rate is in the Krasnoyarsk Region (31%).

The high corruption and bureaucracy of the officials influences badly on the development of the small business, economics and many other aspects of social life. The idea of "corruption effects" (political, economic and social) was suggested by Professor M. Levin, who summarized the ALL-Russian research. This research studies social effects of corruption. As a matter of principle, it is possible to agree with Professor Levin, and say the following about this fact:

– One of the main negative effects of corruption is the increasing of social problems in the country;

– The formation of a new social class in the business society;

– Corruption leads to the increasing of inequality and support unequal redistribution of funds (money) in favour of the charmed circle of the officials and criminals that make damage to the private enterprises and business;

– The entrepreneurs began to think that they are helplessness, naked to the crime and corruption in the authorities, many businessmen don't believe in rightness.

– The social strain in the society is growing that can lead to unemployment, strikes, salary and social relief non-payment.

Corruption is dangerous for every society, especially for a society that is beginning to build market economy. It influences very negative upon the development of market relations, undermines authority of the government, stops the realization of their positive decisions, and makes damage to ethics and morals in the society. Corruption is especially dangerous for the small business development, because the most of labour force is occupied in this sphere. New economic relations in our society mean the struggle against bureaucracy with the help of democracy: actual participation of businessmen due to public associations for formalization, taking and executing decisions, and inclusive of public cases.

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THE DEFINITION OF INVESTING LEASING MECHANISM

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The succsessful realisation of the market strategy of Russia is closely connected with activisation of investment processes, what is explained by the existing scientific-technological and technic delay from the world market leaders in the questions of infrastructure and technology.

The primary task for the solution of the given problem is the question of providing the process of market economy reforming with the large volumes of resources, and first of all-financial resources. It is evident, that, the scarce abilities of russian enterpreneurs concerning the direct financing of capital costs makes the necessity of search of new progressive nontraditional forms of investment activities. As so as traditional (extensive) mechanisms of investment of such scales projects, for example, attracting of loan capacities into the investment project as the direct long term investing credit don't allow to tell about high rates and efficiency of business processes.

The solutions of the tasks, problemed by market strategy of Russia, are founded in the using of synergetic effect: from one side; effective business-processes, from another – effective investments. That's why the special

meaning in the practic work according the structure reconstructing of Russian economy is devoted to leasing, as the most important element of government investing policy, which includes accompanied private, group and public interests. The given form of the investment activity allows to the economis subject to provide the simultaneous improvement od active conditions, technologic base and general finacing-economic condition. It happens thanks to the ability of circulating assets and concentration of costs for financial capital investments, what provides the largest stability of financila flows, in comparison with the purchase with at the own costs. The efiiciency of multiple using of leasing on economy is determined by its capacity to activate private investments into the production field, improves financial condition of economic subjects and increses the competitive business abilities in a whole.

According to the current opinion, leasing mechanism has dual base and containes the the parts of credit and rent activities. Ant the more detailed analysis of leasing operations shows the presence of features of investment relations:

- irreversibility, connected with the temporary lose of consumer capital value (for example liquidity);
- waiting for increasing of the initial level of wealth;
- vagueness, connected with sending the results into long-termperspective.

And at the same time, the investment part of leasing has the number of advantages:

- long terms of financing;
- flexibility in the managing of financial flows;
- flexibility in planning and further using of investment schemes.

As a form of organisation, leasin is equal to the real investments (physis capital investments), as it is the special kind of enterprise activity, directed to the investment of temporaly free financial resoueces into specially required ownship, given for the payment on the contract leasing base to persons or juridical person for the enterpreneur purposes.

Investment part of leasing is determined by the relationship of two subjects, having diametrically opposite interests. At this time the aims for leasing-giver and leasing-receiver have much in common with the aims of investment process: the investment of free financial resources into non-convercial actives with the aim of their long-term using.

The relationships with the participants of leasing dealing depend on the base terms of economi subjects activities and determine the necessity of forming and making the appropriate macro and micro realities of investment strategies.

With the macroeconomic positions leasin allows to create new actives in a real economic sector: leasing-giver and leasing-receiver come into relations concerning the capital, but not in monetary but in producing form, as in the base of leasing we can find the passing of the ownship.

On the micro level the deceision of realising that or another leasing scheme depend on the profitability of definite projects and money flows connecting with them. Consequently, the problesm of leasing using can and must be explored in the context of investment managing.

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THE STRATEGIC ANALYSIS OF MONEY FLOW OF COMMERCIAL ORGANIZATIONS

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The article is devoted to the questions of organization of strategic analysis of money flows. The problems of the determination to the essence and specific particularities of the strategic analysis as a whole are here described. Much attention should be given to the building of the system of the strategic analysis money flow.

In condition of market economies and new forms of management many commercial organizations face with some problems that never arose before. One of them is the operative and strategic management of money flow in enterprises. Making strategies expects orientation on certain future (forecasted) period;

therefore specific methods and receiving the analysis are necessary. As a rule such methods are not used in financial analysis money flow, realized as the financial reporting of enterprise. Since the financial analysis is mostly oriented on study event and the fact of economic activity already happened and revealed in the financial reporting, rather then on future forecasted economic operations, and recently, in theories of the economic analysis it is more and more often possible to meet the reference to the strategic or forecast analysis.

So, Gilyarovskaya L.T. considers that in modern conditions the strategic analysis gains special value, but the intensification of before-production studies, analytical-prognostic accompaniment occupy the leading place in the mechanism of the strategic management [1]. In her opinion, the analytical-prognostic work is conducted on such directions as: marketing studies; the analysis to situations in company; the analysis (scanning) of external ambience.

Selezneva N.N. and Ionova A.F., classifying analysis by periodicity, select perspective prognostic, preliminary analysis. As such analysis they consider the trend analysis (the analysis trend developments), where every position of reporting is compared with beside factors of the previous period and trend is defined [2.p.73.].

Alekseeva I.V., considering questions of the shaping account-analytical ensuring of the strategic account, notes: «The strategic analysis precedes production strategic plan. On the basis of the strategic analysis alternative variants for business activity are worked out ." [3]

The essence of the strategic analysis consists of that due to the preliminary study of the established trend, characterizing current financial condition and factor, influencing on change the financial standing of the enterprise, motivate importance of the key factors, defining financial condition of the enterprise and its financial stability in the future with positions of their correspondence to purpose developments of the enterprise in condition of changing external and internal ambience and under influence of taken decision.

The practical importance of the strategic analysis is concluded in that it allows:

- raise efficiency of management enterprise to the charge of the ensuring of co-ordination long-term and short-term goals of enterprise development;
- beforehand reveal, insofar main trends of supposed activity correspond to the general problem, raised to the enterprise;
- in good time value, insofar factors of the financial plan correspond to the internal possibility of the enterprise and conditions of the external ambience;
- prevent inefficient using of resources;
- characterize the prospects of the growing.

One of the directions of the strategic financial analysis, certainly, is a strategic analysis of money flow in enterprises and organizations.

Particularity of the strategic analysis money flow is necessary to reveal clearly and value influence as external, so and internal factors, influencing upon the size and intensity of money flow, as well as the need to comprise analysis of temporary features, that is to say, to take into account the postponed payments, conduct not only the analysis of the current moving of the bankrolls, but forecast them for necessary length of time (the future periods on time).

In order to make money management more efficient, during the strategic analysis of using the bankrolls it is necessary to bear in mind not only money themselves, but their equivalents. The equivalents of the bankrolls are current assets, which can be circulated in bankrolls in a short period. They present itself short-term, high-liquid investments easy reversible in bankrolls, with small risk of the change of value. However, the possibility of circulation of these equivalents in bankrolls has an element of uncertainty. If total account of all these facilities is a subject of the accounting, that such notions as their liquidity, value with position of the repeated circulation or exchange are the object of the strategic analysis.

The distinguishing features of the strategic analysis money flow are:

- a strategic analysis money flow provides strategic decision making;
- it is based not only on available information (as usual financial analysis), but also on information having restricted access and

external information (indexes, stock rates, factors to inflations, marketing studies of rivals);

- is founded on information of the system of the strategic money flow account of enterprises;

- not available to external users report information;

- a big part of information and factors of the strategic analysis of money flow has accounting predicting nature.

The main methods of the strategic analysis of money flow, in our opinion, are SWOT-analysis, PEST-analysis, SNW-analysis, portfolio analysis, scenario analysis and analysis of financial factor. Using exactly these methods will allow as a result of this analysis to forecast change of money flow in organization under favourable, unfavourable and neutral situation. On the basis of the given strategic analysis of money flow, the enterprises get a real possibility to actively use budgeting of money flow in practice, not limiting only shaping of one budget of the bankrolls moving, but also forming three of its varieties with provision for possible change of situation under influence of external and internal factors.

During the strategic analysis the main attention must be paid to the result of activity of the enterprise in past (herewith the estimation to reliability received results has a great importance), as well as the external and internal factor, which can greatly influence upon it.

The strategic analysis oriented on forecasting of the leading indexes to financial and economic activity of the enterprise in the future, coming from available strategy of the development considering the main trend of current changes in firm and based on integrated system of the account (financial, management, strategic) possible to name the intra-economic strategic analysis. Defining importance for given type of the analysis has a discovery and estimation of the internal factor of influence such as: marketing policy; production potential; financial strategy (policy of shaping of capital circulating and sources of its financing; system of shaping and distribution of financial results) and others. That is also important that consideration of specified factors is reasonable to execute estimating strong and weak sides of the enterprise.

The strategic analysis oriented on forecasting of the leading indexes to financial and economic activity of the enterprise in future, coming from forecast estimation of the key factors from the position of their correspondence to purposes of the enterprise development in condition of changing external ambience, under influence of external factor possible to name the external strategic analysis.

When considering the external factor, which influence can be essential for future financial condition of the enterprise, should pay attention to trends of the total economic conditions: condition on capital market; accessibility of financial resource and level of percent rates; expected rates of inflations; condition on exchange market; the branch particularities (condition in branch and a place of the enterprise in it , state of money-market, concentration of the buyers, competition, preferences of users and others.).

The result of the strategic financial analysis is a forming of probabilistic judgment about future financial condition of the enterprise, which is necessary for taking the identical management decisions and well-timed correcting of strategy and tactics of the enterprise development.

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Materials of the Conferences

TENDENCIES OF ETHNO - CULTURAL DEVELOPMENT IN THE BELGOROD REGION

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There were different periods in ethnic history of Russia: unhurried course of ethnic processes of antiquity was followed by formation of united national and cultural area, which occurred within the limits of centralized state formations - Kievan Russia, Muscovy, Russian Empire, and the Soviet Union. That happened at the time of feudal division in XIII-XIV centuries, social, political and economic instability in XVI-XVII centuries and at the end of the 20th century. Gradually a national identity has formed, which influenced upon economic, political and cultural institutions of society and the whole complex of traditional Russian culture. Social, economic and cultural characteristics of southern Russian border region, and its position in the system of national links were a matter of primary importance for defining long-term perspectives of the State's development.

Modern national and cultural map of the Belgorod Region has been actively shaping since the period of secondary colonization of the Dnieper-Don interfluve. It was happening against the backdrop of strengthening struggle for authority in the region between Russia, the Polish-Lithuanian Commonwealth and the Crimean khanate.

However, some investigators trace more old processes which occurred in the area: archeological and anthropological evidences found in the Dnieper, Don, Oskol and Northern Donets valleys gave a possibility to trace direction of ancient migrations, define the character of interaction and even a medley of different groups of population, as well as mark special features of forming economy and everyday life. [1] Within the limits of ancient Russian State the north Slavs, Khazars, Pechenegs, Polovtsian and other nomadic tribes took part in ethnic consolidation and assimilation. [2] In the history of the Russian Orthodox Church there is a reference to the Belgorod eparchy, which existed since XII century and popularized Christianity among residents. The revival of an underground monastery in Holki is an original confirmation of this fact. Priests consider the monastery to be created in the middle of XIII century, when monks ran away from the Kievo-Pecherskaya lavra because of the Mongolian danger. They chose these cretaceous steeps for their new residence.

Originally the population formed as polyethnic. Many elements appeared in the culture proving that the territorial development was not isolated, but involved in the evolution on European and Eurasian scales. For example, these features could be found in the times of the great migration: many treasures of coins and domestic items have been found, proving that local people were interacting with Germans, whose trade routes ran through southern Russian steppes. A compound three-part horn comb with an ancient runic inscription on top has drawn the scientists' attention. The inscription - female name "Gunta" - was made with a sharp cutting object. Finno-Ugric routes are also present in the names of numerous local rivers, gorges and forests; local dialects maintain some evidences of contacts with ethnic groups of European and Asian origin. [3]

As everybody knows, Tartar invasion interrupted the formation of single Old Russian nationality, but it greatly influenced on the character of ethnic processes in southern Russia: two different ethnic processes entered into conflict. If the Slavs were Europeans, the invaders in their turn belonged to another race - they were Mongolians. The language of the Russian people was one of the languages of the Indo-European family, whereas Tatars spoke languages of Chinese and Tibetan family. Their ways of life were also different: Russians led a sedentary life, they improved agriculture, cattle-breeding, trade and commerce; the others were nomads and herdsmen who satisfied most of their needs by invasions and plunders. During that period migrations were necessary and

violent: Mongolian conquerors forced a considerable part of the Slavs and their neighbors out of the southern Russian steppes to the north and north-west, those who stayed were assimilated. The tartar words appeared then in the toponymy and remained until now: Aydar, Bityug, Usmani, Hava; today we can notice the influence of this culture in household items, everyday speech; the folklore of the Belgorod Region keeps some legends about burned cities and captivities.

In the period of the second colonization in XVI-XVII centuries the Dnieper-Don interfluve was actively digested by Russian settlers, but Ukrainians also migrated here. This resulted in a sort of a compromise: Cossacks-Chercassians were allowed to settle on the Russian territory, provided they accept Moscow citizenship and draw duty at the southern Russian borders. Free Russian and Ukrainian settlers appeared at the territory of the Belgorod Region practically at the same time; however Russian people had advantage in the clash of different colonization currents due to the state support. Belarusian colonization of Russian steppes went on at the same time, but it was not of a large scale. Many Ukrainian settlements were established in the upper reaches of the Voksla and the North Donets rivers, in the river basin of Nezhegol and Oskol. The Ukrainian settlements were usually located within Russian colonies in form of "nests" or wide zigzag zones. (The materials of the first General census in 1897 show that in the Belgorod region the Ukrainian population lived in the following districts: Biryuchansky district - 70,7%, Valuysky district - 51,1%, Grayvoronsky district - 60,4%, Novooskolsky district - 51,8%, Korochansky district - 34,5%, Belgorod district - 24,1%).[4]

In XVII century mass migration of peoples mostly came to an end and the ethnic map of the Belgorod Region was finally formed. The General censuses, organized in XVIII-XX centuries, did not record new ethnic groups which appeared in abundance, and the Belgorod District was developing in the framework of the all-Russian development. Using their traditions, experience, working habits Russian people significantly contributed to the formation of agriculture and culture in the colonized region, adopting a great deal from other nationalities who also took part in the region's development. Cross-cultural interaction between the Slavic nationalities is especially visible in the dwelling organization, traditional cuisine, dialects, musical folklore, holidays and ceremonies.

At the end of the 20th century problems, accumulated in social, political and economic spheres, began to influence upon ethnic relations. Residents of the Belgorod region were among the first in the country who saw and realized their consequences. Immigrants came from Central Asia, Transcaucasia, and later from Ukraine, where the economic situation has been worsening from year to year. Coming in great numbers, they stayed in the region, offering their service in different spheres of manufacture, education and culture. Over the last 10-15 years they greatly influenced on the demographic situation in the region: the correlation of mortality and birth rates has changed towards the birth, also due to immigrants. Life proves that regulation of ethnic processes can only be successful when it's based on knowledge about their general regularities.

Thus, over a period of all ethnic history the population of the Dnieper-Don steppes and forest-steppes has been involved in the ethnic processes on European-Asiatic scale, and the territory of the region has been developing dynamically and as an integral part of the Eurasian world.

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QUALITY AND SAFETY OF GENETIC TESTING IN AUSTRALIA AND NEW ZEALAND: A REVIEW OF THE CURRENT REGULATORY FRAMEWORK

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This paper provides an overview of the regulation of quality assurance for genetic testing in Australia and New Zealand and outlines the steps currently being taken to critically appraise and improve the regulatory framework in each country. It aims to contextualize this framework within the broader context of quality and patient safety concerns; and to draw together the concerns and recommendations of the various organizations that have been working to improve quality assurance in this area.

Background

Genetic tests have the capacity to generate information that may have a profound effect on the tested individual.Test results may affect the individual's treatment decisions, and choices about reproduction, as well as having potential implications for his or her family members.Given this, it is vital that genetic testing occur within a framework that promotes and protects patient safety and well being. One aspect of this framework is quality assurance, which refers to measures to ensure the quality and consistency of genetic testing. The purpose of this paper is to provide an accurate, up to date picture of the current state of the regulatory framework governing quality and safety of genetic testing in Australia and New Zealand. We hope that, given the ongoing reviews of and changes to this regulatory framework, this summary will provide a useful snapshot of the current regulatory environment for those working with or interested in genetic testing and patient safety.

Genetic testing in Australia and New Zealand

Genetic tests are preformed by a range of private and public organisations in Australia and New Zealand. As of 2005, over 220 genetic tests were available in Australia and 45 laboratories were providing genetic testing services [3]. These laboratories are generally attached to or affiliated with a public hospital or university. Tests are also provided by private genetic testing or pathology laboratories. In addition, some government departments have laboratories that conduct genetic testing, for example forensic laboratories. Some tests are also carried out in research laboratories, particularly tests that are still in the research phase or for which there is little demand. Seven laboratories in New Zealand offer diagnostic testing for approximately 75 genetic disorders [3]. The two main laboratories are the Diagnostic Genetics Department at Auckland City Hospital, and Canterbury Health Laboratories, Christchurch. Outside major city centres, testing services are provided through outreach clinics. The current range of genetic

tests available in New Zealand depends on clinical demand, the focus of individual laboratories and the available funds from each District Health Board (DHB).

What is quality assurance in genetic testing?

Quality assurance in genetic testing refers to measures to ensure that laboratories adhere to high standards of care and undertake testing that is justified and accurate. Quality assurance in genetic testing fits within the broader of concept of patient safety and wellbeing, as it is one element of a range of strategies used within the healthcare system to ensure that patients receive appropriate, effective treatment on a voluntary and informed basis. These strategies include pre-and post-test measures, such as effective identification of individuals at increased risk of a genetic disorder, genetic counselling, appropriate privacy and confidentiality regulation and/or legislation. Genetic tests can reveal highly personal information about an individual and in many cases other family members, hence appropriate measures should be in place to protect the privacy and confidentiality of the results, to prevent unauthorised access and possible misuse of this sensitive information. This paper focuses on the regulation of quality assurance of genetic testing, so only the test stage of the testing process is examined in detail. At the test stage, measures to ensure quality assurance fall into two categories – (1) the safety, accuracy and utility of a test; and (2) the competency of the laboratory and its staff in performing that test. The safety, accuracy and utility of a test are important issues in patient safety because a lack of any one of these characteristics may lead to the patient receiving misleading or unhelpful information. For example, there is debate about whether genetic tests should be preformed if there is not available treatment for the condition. The genetic condition of Huntington's disease provides a relevant example. Although there is currently no cure for Huntington's disease, some at risk people choose to have the genetic test and use the information to inform his or her reproductive decisions. Tests are judged in relation to analytical validity, clinical validity, and clinical utility to ensure they are safe and accurate. Analytic validity is the ability of a test to detect the trait it seeks to measure. Clinical validity is the capacity of the test to predict a specific clinical outcome. Clinical utility refers to the actual usefulness of the test in improving health and well-being of the persons tested and largely rests on whether the information provided by the test can be followed by effective and safe preventive or therapeutic interventions. The second aspect of quality assurance at the test stage is laboratory competency. If tests are not performed correctly, using the right equipment, or the laboratory staff lack the skills to perform the tests, then the results may be inaccurate. Further, the laboratory should be competent in managing samples and results, maintaining confidentiality and privacy, and in delivering results appropriately. Administrative failures may lead to the loss of results, mix ups or breaches of privacy and confidentiality, harmful to the patient's interests. It is therefore important to ensure that laboratories are competent to undertake and manage the tests they offer.

Quality assurance regulation general framework

Genetic testing in Australia and New Zealand is subject to the more general scheme of laboratory and test accreditation, although some specific regulations and guidelines do apply. This reliance on a generic regulatory framework is largely due to the fact that the aspects of genetic testing and genetic information that differ from general testing and medical information are most relevant at the pre- and post-test stage. For example, genetic counselling is necessary prior to, and following, some genetic tests due to the particular ramifications of the results, but this is regulated largely through guidelines for professionals working in genetics, rather than at the test stage [see, eg, [4]]. This general quality assurance scheme is comprised of legislative requirements, accreditation standards, and guidelines developed and administered by a number of organizations. In both Australia and New Zealand, the national government acts as the primary regulatory body for healthcare services through a national health department in collaboration with a number of government advisory bodies. Regulatory bodies also include laboratory and professional accreditation bodies, and consumer protection agencies. In addition, professional organizations act as advisory

bodies, offering independent guidelines and standards of practice. There is some overlap between the Australian and New Zealand schemes. ***General healthcare framework for Australia***

The regulatory framework governing the provision of genetic tests sits within the broader healthcare system and so it is important to have a sense of the way health services are provided and funded in Australia and New Zealand. The Australian health care system is largely regulated (and partially funded) at the State and Territory level; however the Federal Government also provides funding and has a regulatory role. Medical services are provided through both the public and private sectors, and public subsidies (Medicare benefits) are available for many services. The Federal government regulates the provision of pathology services only indirectly through the administration of the Medical Benefits Schedule (MBS) by withholding subsidies for pathology services from laboratories that are not appropriately accredited [[5], p4]. It also regulates specific *tests*, whereby only accredited tests are subsidised. The States and Territories do have the power to regulate pathology services, however only Victoria has enacted specific legislation in this area [6]. The test and laboratory accreditation schemes are outlined below; however Figure 1: Regulation and accreditation pathways for genetic testing in Australia provides a summary of these schemes and their interaction.

General healthcare framework for New Zealand

The Ministry of Health Manatû Hauora (MOH) is the New Zealand governmental agency that issues guidelines and policy for medical services throughout New Zealand [7]. The MOH distributes funding to District Health Boards [8] which are in turn responsible for funding and delivering health and disability services in their district. DHB laboratories perform the majority of genetic tests, and are usually based in public hospitals.Testing services and laboratories are regulated to some degree by the MOH as part of its responsibility for maintaining the National Health Service. The MOH regulates some requirements for laboratory quality and auditing, as well as defining the mechanisms through which laboratories are funded [[9], p9]. Laboratory accreditation in New Zealand is administered by an agency called International Accreditation New Zealand (IANZ). The New Zealand schemes for introducing new tests and ensuring laboratory quality standards are discussed below, however the regulation and accreditation pathways are also summarized in Figure 2: Regulation and accreditation pathways for genetic testing in New Zealand.

Test accreditation

Australia

In Australia, the use of tests is regulated partially through funding incentives provided by the Federal Government. For tests to attract a government subsidy, an application must be made to the Medical Services Advisory Committee (MSAC) [10], which advises the Federal Government on new medical technologies and procedures. MSAC bases its assessment on the safety, effectiveness (including validity and utility), and cost-effectiveness of the test in accordance with the MSAC guidelines [11]. MSAC makes recommendations to the Federal Minister for Health and Ageing, who then decides whether the test should receive public funding. If successful, the test will be listed on the MBS and Medicare benefits will be available.This system creates an incentive for laboratories to provide only tests that have been accredited, as otherwisepatients will be unable to apply for Medicare benefits tooffset the cost of the test. It does not, however, preventunaccredited tests from being offered and therefore does not wholly protect patient safety.Further, the MSAC submission process can be both timeconsuming and expensive, which may discourage the submission of some tests where the process may not be costeffective.Completing the MSAC application process can be labour intensive and time consuming as applicants must attend a pre-lodgement meeting and then complete a forty-three page application form. In completing the application, the applicant should make reference to the 2005 guidelines which are 100 pages long. This may discourge manufacturers of diagnostic tests for rare genetic conditions and a small potential market from applying toMSAC for Federal funding [40].

New Zealand

Unlike Australia, New Zealand has not introduced a formal system for validating new genetic tests and the MOH has no formal role in assessing new tests. Rather, new tests are introduced in response to clinical demand, or as a result of the individual interests of each laboratory [[9], p8]. Each DHB is responsible for funding genetic tests, and are therefore responsible for the quality of testing in their regions. Genetic tests are also not listed on the Laboratory Services Schedule, which lists tests available for public funding in New Zealand, as determined by the Laboratory Services Advisory Group. There is also no advisory body in New Zealand responsible for determining whether a genetic test should be publicly funded [[38], p13]. Despite this lack of formal assessment of new tests, those that are offered in New Zealand tend to be for common genetic conditions and are usually well validated. Where a patient requires a

test for a less common condition, thesample will often be sent to a laboratory outside New Zealand [[9], p9]. Further quality assurance is provided through the laboratory accreditation scheme, as a laboratory cannot receive healthcare subsidies for any test unless it has received IANZ accreditation to perform that test [[9], p13].

In vitro diagnostic devices

It should be briefly noted that a new scheme for regulating in vitro diagnostic devices (IVDDs), which will cover some genetic tests, is being developed by the Australian Therapeutic Goods Administration (TGA). Development of the scheme was initiated in January 2002 by the TGA, and an agreement in principle to the proposed regulatoryframework for IVDDs was made by Australian HealthMinisters' Advisory Council (AHMAC) members on 23October 2003. An outline of the framework can be foundat the TGA website [47]. The TGA is currently developing risk-based classifications for IVDDs, and this scheme will include genetic tests. An IVDD will be placed in one of four risk classes:

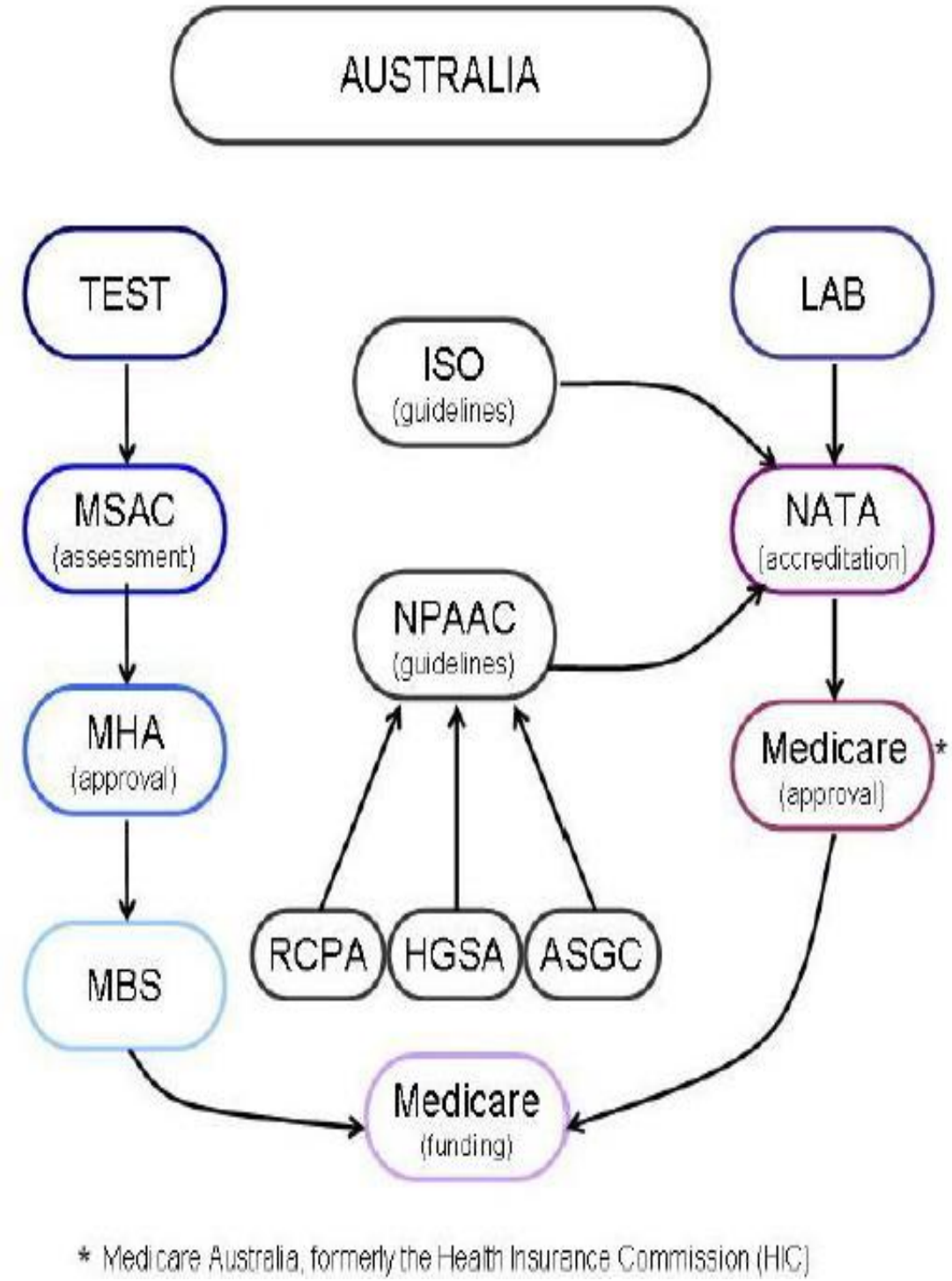

Figure 1
Regulation and accreditation pathways for genetic testing in Australia.

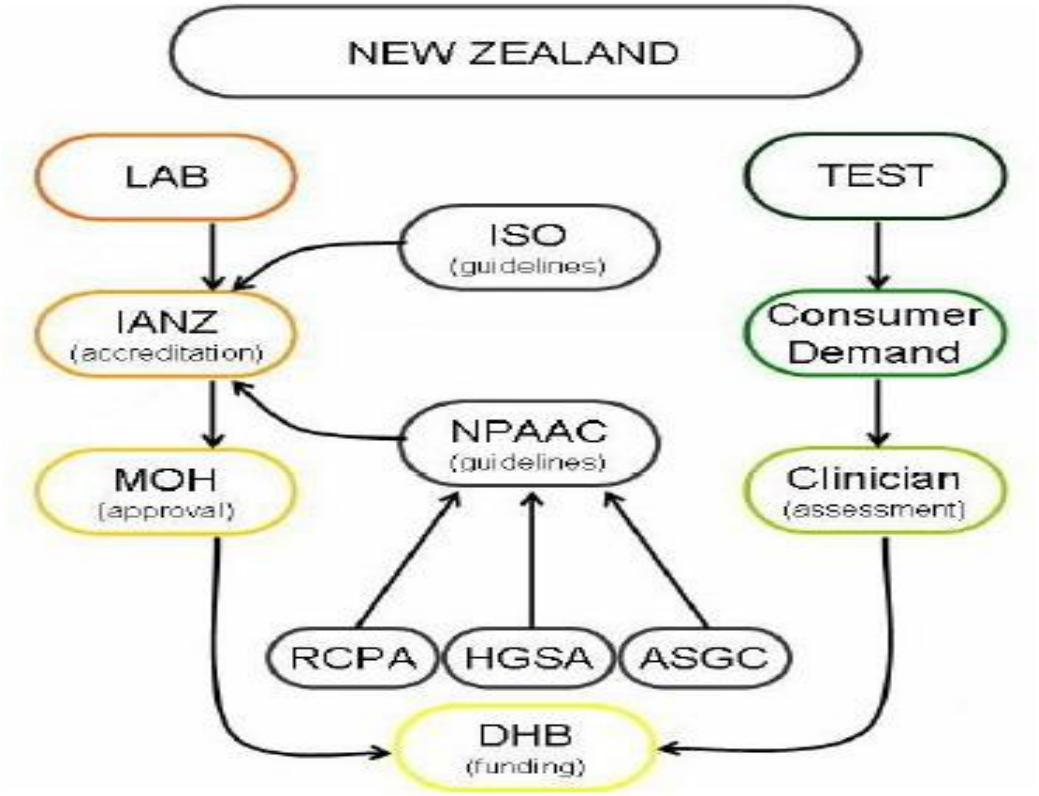

Figure 2
Regulation and accreditation pathways for genetic testing in New Zealand.

• Class I: no public health risk/low personal risk;

• Class II: low public health risk/moderate personal risk;

• Class III: high personal risk/moderate public health risk;

• Class IV: high public health risk.

The TGA has given examples of genetic tests that will fall into some of these classes. Class II IVDDs are tests "that detect the presence or exposure to infectious agents that are not easily propagated in the Australian population or that cause self-limiting diseases" and present a moderate individual risk, where the test is not intended to be the sole diagnostic method or "where an erroneous result rarely puts the individual in immediate danger". This will include some genetic tests such as thrombophilia mutation screening tests.Class III IVDDs are tests that provide the "critical, or sole, determinant for the correct diagnosis", where "an erroneous result would put the patient in an imminent ifethreateningsituation, or would have a major negative impact on outcome". The TGA also states that these are tests that "may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures". This class of IVDDs will include predictive genetic screening tests for conditions that will usually have "a substantial impact on the life of the individual", such as tests for phenylketonuria (Guthrie test), Huntington's Disease, Cystic Fibrosis [47].

Some comparisons

The major difference between the Australian and New Zealand systems is that Australia has developed a centralized process for assessing new genetic tests before they can be offered to patients. Such a system is useful, as it ensures that all tests are consistently evaluated for analytical and clinical validity as well as clinical utility before they are provided to the public. However, it appears that in New

Zealand, for the most part, only tests that have been well validated either within the country or elsewhere are offered, and at present there is no evidence that this lack of formal regulation is highly problematic. This may be because health services in New Zealand are more locally integrated than their Australian equivalents.

Laboratory accreditation

Australia

The Federal Government uses funding incentives toencourage laboratories to become accredited (and hencemaintain adequate laboratory standards). To receiveMedicare payments for medical services, a laboratorymust be accredited in the relevant testing services, complywith the NPAAC guidelines and be designated an Accredited Pathology Laboratory. Accreditation of testing services is administered by the National Association of Testing Authorities, Australia (NATA). NATA is an independent, private, not-for-profit company operating as an association. It is owned and governed by its members (registered laboratories) and representatives from industry, government and professional bodies (such as the Royal College of Pathologists). NATA, as a member of the Asia-Pacific Laboratory Accreditation Cooperation (APLAC), regularly participates in audits by, and of, its mutual recognition partners in Europe, North America and the Asia-Pacific region. NATA operates an accreditation scheme for laboratories and is the Federal Government-endorsed accreditation body for establishing competent laboratory practice. This was outlined in the Memorandum of Understanding between NATA and the Commonwealth government [13]. Laboratories apply directly to NATA for accreditation in types of medical testing. NATA's medical testing accreditation scheme is based on the relevant guidelines issued by the National Pathology Accreditation Advisory Council (NPAAC). NPAAC consists of representatives from the DHA, the State and Territory departments of health, and from peak professional organizations including the Royal College of Pathologists of Australasia (RCPA) and the Human Genetics Society of Australasia (HGSA), among others. NPAAC advises the Commonwealth, State and Territory Health Ministers on matters relating to the accreditation of pathology laboratories. NATA accreditation standards are developed with reference to international standards (such as ISO) for laboratory competency in consultation with the RCPA. Such international standards are incorporated by a requirement that NPAAC guidelines be read "with" the standards, such as the *Laboratory Accreditation Standards and Guidelines for Nucleic Acid Detection Techniques* which are to be read with AS ISO/IEC 17025:1999, *General requirements for the competence of testing and calibration laboratories*. This adds an extra layer of quality assurance to the requirements put in place by NATA and NPAAC. Once laboratories apply for accreditation, NATA conducts an inspection to determine whether they satisfy NPAAC requirements and, if successful, they then become members of NATA. They must undergo periodic future inspections to maintain accreditation [[5], p2]. In accrediting a laboratory, NATA endorses its competency to undertake testing, which can include genetic testing. Professionals from the pathology industry volunteer to act as peer reviewers for NATA accreditation assessments. Peer reviewers undergo accreditation assessment training and work with a NATA staff officer to ensure objectivity and consistency [[5], p11]. To obtain NATA accreditation and receive Medicare benefits laboratories must comply with the standards and guidelines released by NPAAC [14]. NPAAC standards and guidelines cover many aspects of laboratory practice including: laboratory ethics; quality systems; staffing, supervision and consultation; facilities; test ordering, analysis, and follow-up; occupational health and safety; and internal and external auditing for quality assurance [15]. In particular, NPAAC's *Standards for Pathology Laboratories* requires that patient wellbeing and confidentiality be the primary considerations of the laboratory when performing tests [[15], Standard 1]. This means that no person should disclose patient or test information to anyone other than the requesting medical practitioner, or other medical practitioner currently treating the patient, except in some defined circumstances outlined by state and federal privacy legislation. NPAAC requires that human samples, tissues and remains be treated

with due respect. Finally, it is the responsibility of the laboratory to ensure that the quality of their work is not affected by any improper pressure, be it financial, commercial, or otherwise. NPAAC standards require laboratories to undergo external quality assurance testing programs, such as those provided by the RCPA, and to perform to an acceptable standard [[15], Standard 9]. Data from these external programs are made available to NATA during assessment [[5], p14]. Where there is no external proficiency program available, laboratories are required to undergo inter-laboratory comparisons and/or analysis of reference and control materials [[15], Standard 9]. Once accredited, to receive Medicare benefits for tests, a laboratory then must apply to the Minister for Health and Ageing (the Minister) via Medicare Australia for approval to become an Accredited Pathology Laboratory (APL), as only APLs may obtain Medicare benefits for pathology services provided [[12], s 16A(2)(b)]. The approval process and requirements are is provided by the *Health Insurance Act 1973* (Cth) (HI Act) [[12], s 23DN(1), (2)]. Accreditation decisions must be made in accordance with the HI Act and the *Health Insurance (Accredited Pathology Laboratories-Approval) Principles 1999* (Cth). Laboratories applying for accreditation must have undergone a NATA inspection prior to application and include the NATA inspection report with their application. Only those pathology services approved by NATA will be eligible for Medicare benefits if accreditation is obtained. Without NATA accreditation, and subsequent approval of the laboratory and personnel by Medicare Australia, laboratories are unable to access the benefits of Medicare payments for their services. In the case of a breach of the principles outlined by NPAAC, NATA, and Medicare Australia, Medicare benefits and accreditation may be removed. Inability to provide tests at subsidised rates may adversely affect a laboratory's capacity to provide competitively- priced tests, and hence the revocation of Medicare benefits is a strong incentive for laboratories to achieve accreditation. Until recently, Victoria had an independent structure for accreditation of all pathology laboratories in the state, regardless of whether they seek Medicare payments [16]. The Pathology Services Accreditation Board, on behalf of the State Minister for Health, governed accreditation procedures and legislation as defined by the *Pathology Services Accreditation Act 1984* (Cth) in accordance with NPAAC standards and the NATA/RCPA scheme [[17], s9]. However, this act was repealed in 2003 by section 14(1) of the *Health Legislation Amendment Act 203* (Vic), and the Board consequently dissolved in January 2004 [43].

Genetics-specific regulation and accreditation

NPAAC standards do make some specific provisions for the unique challenges raised by genetic testing. Previously, under the *Laboratory Accreditation Standards and Guidelines for Nucleic Acid Detection Techniques* 2000 version, NPAAC recognised that "the implications of laboratory diagnosis of genetic disease are different from those of many other areas of laboratory testing" and as a result draws a distinction between two types of testing – diagnostic genetic tests (Class A) and predictive, carrier and prenatal genetic tests (Class B). For Class A tests, only verbal consent is required and there is no requirement for pre-test counselling. By contrast, Class B tests are carried out on non-symptomatic patients who must receive preand post-test counselling and must provide formal, written consent. In addition, laboratories were required to take responsibility for ensuring the formal consent has been obtained and counselling provided. For Class B tests, where the laboratory suspects that proper consent has not been obtained, it is required to contact the referring practitioner to ensure informed consent has been obtained before it may undertake testing [[20], para 1.2]. Under the same standard, laboratories are prohibited from providing patient-initiated tests, such as mail-order testing. This description of DNA testing for inherited genetic disorders – divided into Class A and Class B – has been revised in version 6.1 of the NPAAC standards and guidelines implemented in August 2006 [1,42]. This change was deemed necessary because, a particular test could move between Class A and Class B on a case by case basis, depending on its use and circumstances, which

has caused confusion. The latest draft of the NPAAC guidelines for Nucleic Acid Detection (set to be approved in 2006) has attempted to dispel this confusion by changing the classification system. The Level 1 (standard DNA test) and Level 2 DNA test (complex issues) categorisation allows classification to vary regardless of the test based on the implications of the testing situation.

Level 1 DNA tests (standard) include a) DNA testing for confirmation of diagnosis where the patient has a clinical diagnosis, symptoms, or a family history of an established inherited disorder or any other DNA test that doesn't fall into level 2; b) Neonatal screening programs.

Level 2 DNA tests are considered those tests which could potentially to lead to complex clinical issues. Level 2 tests would include predictive or presymptomatic DNA testing, and tests for conditions for which there is no simple treatment. In these cases, specialised knowledge is often necessary to determine the need for testing (i.e. the test should be requested by a specialist rather than any physician). Level 2 tests should be accompanied by both pre- and post-test professional genetic counselling and may also require specific written consent [[42], Table 1.1].

Version 6.1 of the NPAAC document will require laboratories to review the categorisation of DNA tests for human inherited disorders with the guidance of representative professional bodies. Classification of a test as Level 1 or Level 2 will take into consideration "resources, current knowledge, circumstances, the type of condition being tested for, and the implications of the DNA test result for the patient and family". Laboratories providing genetic testing in Australia are also covered by the influential, if not binding, information papers, guidelines and principles released by the National Health and Medical Research Council which outline some of the ethical aspects of genetic testing [see, eg, [21]], and policies released by the HGSA [22].

New Zealand

International Accreditation New Zealand (IANZ) is the Crown-owned, user-funded authority providing accredit tation for a range of laboratories and related technical services in New Zealand, including pathology laboratories [9]. IANZ Laboratory Accreditation for Medical Testing complies with *NZS/ISO 15189:2003 Medical Laboratories – Particular Requirements for Quality and Competence* [23]. This standard replaced the New Zealand Code of Laboratory Management Practice for all IANZ accreditation as of 1 January 2004 [24]. The IANZ accreditation system and the specialist technical peer-review process include the assessment of laboratory staff. IANZ further requires that laboratories offering genetic testing comply with the Australasian NPAAC guidelines [see list of applicable guidelines at [25]]. In addition, both the HGSA and the RCPA offer quality assurance assessment for genetic tests by carrying out proficiency testing for some common tests [[9], p13]. Many laboratories also participate in College of American Pathologists (CAP), and/or European Molecular Quality Network (EMQN) programs [Personal communication (March 14, 2005) Dr. Karen Snow Bailey, Director of Diagnostic Genetics, LabPlus, Auckland District Health Board, New Zealand]. IANZ has entered into a mutual recognition arrangement with NATA (the Australian accreditation body) recognizing equivalency of their standards of accreditation [26]. New Zealand laboratories are therefore also subject to NPAAC guidelines, as compliance with these is a prerequisite of NATA accreditation. The IANZ reports annually to the MOH. If the ministry is informed of a breach of the IANZ guidelines, action is taken through the funding agreements with the DHBs, rather than by taking action against the individual laboratory. The DHB is responsible for ensuring the quality of the laboratories to which it provides funding [9].

Genetics-specific regulation and accreditation As IANZ uses NPAAC standards, New Zealand laboratories are subject to the same standards in relation to genetic testing as described below. New Zealand laboratories are also subject to HGSA policies, but not to NHMRC guidelines.

Australia and New Zealand overlap and the joint Trans

Tasman scheme

From the preceding discussion, it becomes clear that Australia and New Zealand have

integrated their two quality assurance systems to some degree. This integration is summarized in Figure 3: Integration of regulation and accreditation pathways for genetic testing in Australia and New Zealand. Recently, the two countries took steps towards further integration of their schemes in December 2003 by accepting a joint proposal for a Trans-Tasman agency for the regulation of therapeutic products [[27]; 28]. The proposed agency will replace Australia's TGA and New Zealand's Medsafe, and will include regulation of materials for genetic testing and IVDDs. At the time of writing (August 2006), considerable progress towards establishing the agency, to be known as the Australia and New Zealand Therapeutic Products Agency, had been made. The first round of public consultations were held in June 2006 in Australia and New Zealand and the second round is proposed for September 2006 and a third and final round for March 2007 [46]. According to the Therapeutic Products Interim Ministerial Council, the scheme is expected to commence in the second half of 2007 [49].Establishing the Trans-Tasman agency is an encouraging step. It will improve consistency in practices and streamline quality assurance procedures, which will be particularly important in this region. Samples are often sent between Australia and New Zealand for testing, for example in cases where one country lacks capacity in a particular test, and improved consistency and integration can only further develop quality assurance mechanisms by removing gaps in regulatory coverage. Further, this joint approach will better equip each country to address regulatory issues raised by new, innovative technologies as they emerge [45].

Reviews of regulatory and accreditation systems

Australia and New Zealand have been pro-active in their attempts to identify and address the problems in their systems of quality assurance with respect to genetic tests. Genetic testing is an rea of medical technology that continues to develop rapidly. For this reason, the Australian and New Zealand accreditation schemes are subject to regular reviews to assess whether they effectively ensure appropriate quality standards in genetic testing. These reviews have highlighted a number of areas for improvement. We now describe the findings of recent reviews and present a summary of the common themes of these evaluations. Note that some of these reviews referred to the Health Insurance Commission (HIC), which from October 2005 has been known as Medicare Australia. These references have been left as they were in the original reviews, however all references to the HIC in this section should be taken as now referring to Medicare Australia. The HIC *Annual Report 04–05* provides information on the changes to the Commission and the relevant legislative amendments [[44], Ch 2.2].

Australian reviews

Australian Law Reform Commission inquiry

In 2001, the Australian Law Reform Commission (ALRC), a permanent, independent federal statutory corporation providing advice to the Australian Federal Government on areas of law reform, began a comprehensive two-year inquiry into the protection of genetic information in Australia

(ALRC Inquiry) [30]. The ALRC Inquiry included a review of some aspects of pathology service provision, and identified a number of concerns in relation to quality assurance and genetic testing, including:

• the lack of independent assessment of non-accredited laboratories;

• failure of current accreditation standards to address issues such as informed consent, privacy, and chain of custody of samples;

• the possible provision of genetic tests direct to the public, without proper consent or counselling [[30], Ch 11]. The ALRC made a range of recommendations directed at addressing these concerns. It recommended that:

• An oversight body for issues around genetic testing and genetic information, known as the Human Genetics Commission of Australia (HGCA) be established [[30], Recs 5–1 to 5–9];

• The HGCA should develop codes of practice and advice relating to the provision of technical and ethical standards for genetic testing services provided direct to the public [[30], Recs 11–2 to 11–7];

• The HGCA should develop genetic testing and counseling practice guidelines, in consultation with HGSA, state genetic services, and other interested parties [[30], Rec 23– 2];

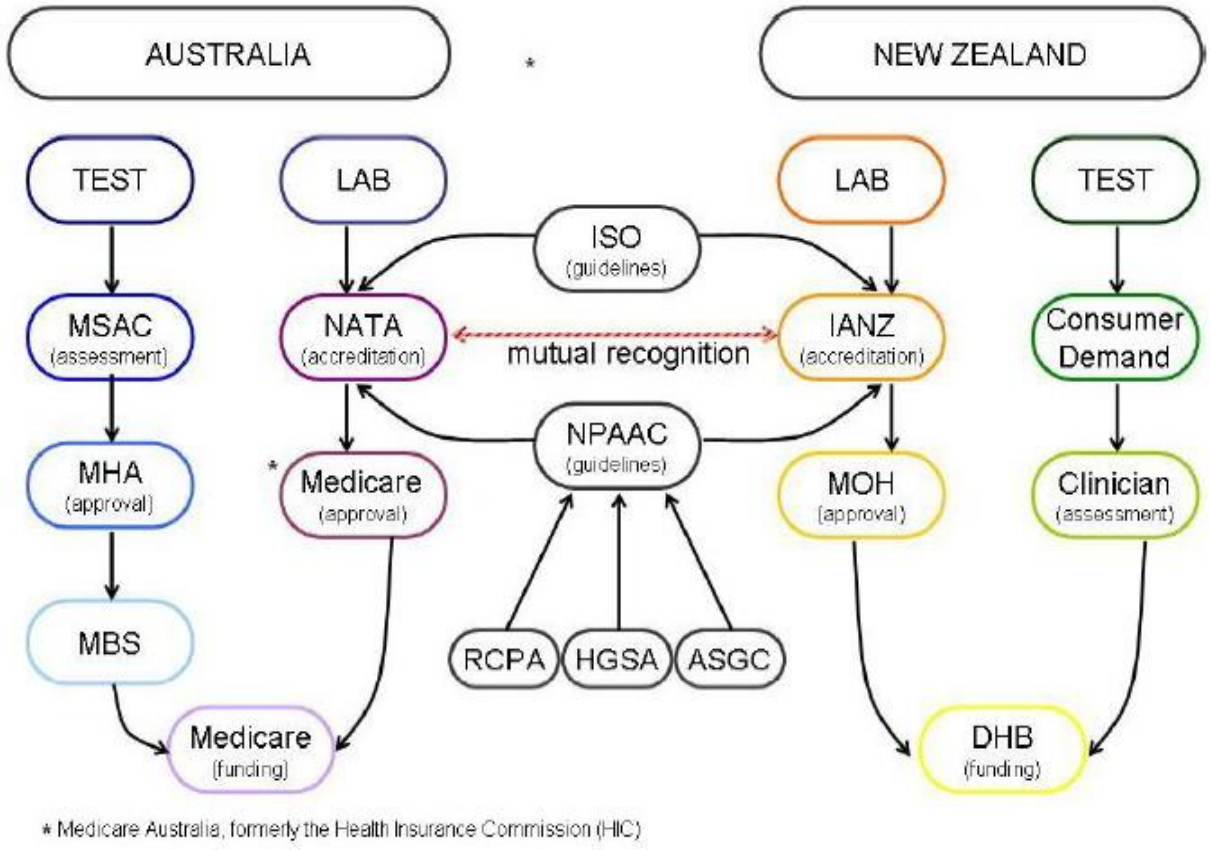

Figure 3
Combined regulation and accreditation pathways for genetic testing in Australia and New Zealand.

• NPAAC should further develop ethical standards for medical genetic testing, in consultation with the NHMRC and the proposed HGCA;

• NPAAC should examine how to assess compliance with accreditation standards in relation to consent, counseling and other ethical considerations; and NATA should develop training programs to equip its officers and peer assessors to verify compliance [[30], Recs 11–2 to 11–4]; •

The Commonwealth Government should amend the *Therapeutic Goods Act 1989* (Cth) to better regulate genetic tests provided directly to the public [[30], Recs 11–2 to 11–5]. To date, only some of the ALRC's recommendations have been implemented. However, one notable success is the Federal Government's commitment in the 2005 Federal Budget to provide $7.6 million over four years to establish an independent expert advisory body on human genetics. The new body, named the Human Genetics Advisory Committee, is now a central committee of the NHMRC [31]. This body satisfies the inquiry's core recommendation for the establishment of the HGCA, and is a significant step towards more effective regulation of genetic testing, including quality assurance. More information about the functions and membership of the committee can be found on the NHMRC website [52]. The Federal Government is currently preparing a response in relation to the remaining recommendations in the ALRC Inquiry report [31].

Department of Health and Ageing reviews

Also in 2001, the Federal Department of Health and Ageing (DHA) commissioned a

major independent review of the Australian pathology laboratory accreditation arrangements (Pathology Accreditation Review). This review was the first comprehensive evaluation of the arrangements since their introduction [[5], p1]. The review found that "the current Australian pathology accreditation arrangements are fundamentally sound and should be maintained" [[5], Rec 2.1]. However, the review also identified a number of areas in which accreditation could be improved. These included: • Lack of Federal power to directly regulate pathology services [[5], p4]. • Delays in current management of non-compliance in a small number of laboratories, which have resulted from delays in arranging or conducting NATA/RCPA assessments; delays in referral of non-compliant laboratories to the HIC; due to NATA's internal appeal process; or due to administrative appeal procedures [[5], ppi, 4]. • As most laboratories are regulated through administration of the MBS, the small number of laboratories that do not seek Medicare benefits are unregulated [[5], pi]. As a result, it is difficult for the HIC to enforce compliance with NPAAC standards within these laboratories [[5], p4]. The Pathology Accreditation Review resulted in 37 recommendations, the great majority of which were accepted by the DHA in its response [32]. Many of these recommendations were detailed and focused on very specific aspects of the accreditation process, therefore only a few more general, overarching recommendations are outlined here. In particular, the Pathology Accreditation Review recommended that an evaluation be made of the costs and benefits of enacting State and Territory legislation to complement the national regulatory system. As the States and Territories have the power to directly regulate pathology services, such legislation could address the lack of regulation of laboratories that fall outside the current accreditation system because they do not access MBS subsidies [[5], Rec 2.2]. The ALRC Inquiry made a similar recommendation [[30], Rec 11–1]. Finally, the Pathology Accreditation Review recommended increasing the sanctions open to the HIC to deal with non-compliant laboratories. The HIC should be able to:

• require that laboratories participate in re-inspection;

• to notify the public of laboratories rated 'Non-Compliant with Moderate or Serious Risk';

• to require laboratories to notify referring medical practitioners and/or consumers of their non-compliant status;

and

• to revoke Medicare benefits [[5], Rec. 6.1].

In relation to the need to identify an organisation or individual with clear responsibility for the oversight of the pathology quality assurance system, the Australian Council for Safety and Quality in Health Care (ACSQHC) has undertaken preliminary work to consider structures that could oversee standard setting and quality monitoring in this area. Therefore, the Pathology Accreditation Review recommended that the DHA allocate responsibility for the oversight of pathology quality assurance systems to a DHA senior officer until the ACSQHC takes further action [[5], Rec. 6.5]. As a result of this review, the Commonwealth Government has announced moves to improve the standards of pathology laboratory testing and to identify laboratories that do not meet required standards [33]. The DHA con firmed in 2003 that the Australian Health Ministers' Advisory Council Group on Human Gene Patents and Genetic Testing was considering the establishment and implementation of an improved quality assurance and accreditation scheme [[30], p339]. The DHA has instigated two other reviews of the regulation of pathology services. One, the *Review of the Commonwealth Legislation for Pathology Arrangements under Medicare*, was completed in 2002 (DHA Review) [34]; the other, the *Review of enforcement and offence provisions of the Health Insurance Act 1973 as they relate to the provision of pathology services under Medicare* (Enforcement Provisions Review) was completed in August 2005 [35]. These reviews examined in detail some aspects of the regulatory framework for pathology services, including enforcement and offence provisions, compliance arrangements, funding and accreditation. The DHA Review noted two main challenges relevant to quality assurance in

genetic testing, to which the Federal Government has responded positively. First, the government is taking steps review the current qualification requirements and the approval process for Approved Pathology Practitioners to ensure, among other things, regular checks on staff competency (in line with Recommendation 11) [[34], Rec. 11] [36]. Second, the new Pathology Laboratory Principles that came into effect on 1 January 2003 act on part of Recommendation 13 to:

• strengthen links between the NATA accreditation process and approval as an APL;

• strengthen the HIC's powers in relation to laboratories operating below standard; and

• develop links between participation in a quality assurance program and notification of the results [[34], Rec. 13, 36].

The DHA Review also considered there was a need for greater enforcement provisions, recommending the establishment of new offences, strengthening of the Medicare Participation Review Committee and "introducing a system of direct administrative action" by HIC [[34], Rec. 14]. In August 2005, Phillip Fox Lawyers released the government commissioned Enforcement Provisions Review report [50]. This Review was commissioned by the DHA in response to recommendations 14 and 15 of the previous DHA Review. The Enforcement Provisions Review makes a series of recommendations aimed at clarifying and strengthening the provisions of the *Health Insurance Act 1973* (Cth) (HI Act). While there is not space here to summarise the wide range of issues addressed in the report, its primary recommendations focus on making it clearer that certain relationships between pathology providers and requesting practitioners are prohibited, and ensuring that appropriate enforcement action is available where breaches occur. In particular, the Review clarifies that provision of, or demand for, financial or other incentives for referral for pathology services breaches the letter and spirit of the HI Act, particularly s129AA and s129AAA (p2 Section 1.11). To give one example, the Review recommends that a Medicare benefit be reinstated to cover the costs incurred by general practitioners in collection of samples for pathology testing (particularly in rural and remote areas) (Recommendation 33), which would prevent the provision of incentives by the pathology provider in the form of disposables for sample collection. In May 2006, the government accepted the bulk of Phillip Fox's recommendations and has and agreed to act on these as swiftly as possible to expedite clarification and strengthening of the enforcement and offence provisions, and simplification of the sanctions process [51]. This will include the recommended amendments to the HI Act, and additions to and consolidation of s129AA and s129AAA (which will likely involve the repeal and replacement of the provisions, rather than amendment). In some cases the government agreed to take action supporting the intent of the recommendation, rather than the specifics proposed by the review. These included Recommendation 2, that the HI Act be amended to enable the HIC to address "serious and imminent risk to public health" by suspending an APL approval without a hearing to the APA. The government agreed, in conjunction with Medicare, to explore options and determine minimum requirements for this action to be taken [51].

National Public Health Partnership report

Until July 2006, the National Public Health Partnership (NPHP) was a sub-committee of the Australian Health Ministers' Advisory Council (AHMAC), established under a Memorandum of Agreement between the Federal, State and Territory governments in 2003 [37,53]. During its operation, the NPHP compiled *An Overview of Public Health Surveillance of Genetic Disorders and Mapping of Current Genetic Screening Services in Australia*, released in October 2002, to summarize the current organization and availability of genetic services, and the legislation in place to regulate these services (NPHP Overview). The report identified a number of issues, and recommended that a national approach be taken to deal with them. The issues it identified that relate to quality assurance in genetic testing were that: • Existing legislation used to regulate genetic testing is not always specific to genetics. Some states rely on general federal regulations that may be used to cover genetic testing. • Although there is widespread voluntary compliance with NPAAC, HGSA, and NATA guidelines, there

are no direct measures to combat non-compliance. • The division of healthcare funding between the Federal Government and State and Territory governments raises issues about ensuring equitable access to tests.

New Zealand reviews

Two major reviews of genetic testing practices have been undertaken in New Zealand in the past three years. The first, a report by Dr Diana Sarfati for the National Health Committee (NHC) [9] released in 2002 (Sarfati Report), provides an overview of genetic testing in New Zealand in relation to international standards of best practice. The report did not focus on identifying areas for improvement nor did it make any recommendations, but did note a number of areas of concern, such as:

• The lack of formal quality control programmes to ensure standards of quality for genetic testing in some laboratories.

• The capacity of current accreditation mechanisms to detect poor laboratory practice.

• The exclusion of research laboratories providing clinical testing from IANZ accreditation requirements, as they may lack quality assurance processes.

• IANZ's lack of power to enforce compliance. For example, there is no requirement for it to contact the MOH when it suspects that a laboratory is not meeting its standards Even when the MOH is informed, its only means of pressing for compliance is funding agreements with DHBs, which are responsible for quality of testing services [9,13,14].

The report also noted that the NHC was working on a framework for assessing new technologies, including genetic tests, that would, among other things, examine their safety and effectiveness [[9], p9]. In 2003, the National Advisory Committee on Health and Disability of New Zealand issued a report for the NHC, *Molecular Genetic Testing in New Zealand* (NHC Report) [38]. This document built on a 1995 report to the NHC on priorities for genetic services in New Zealand [39], and highlighted the areas requiring further development to meet the growing demand for genetic services and to ensure the equitable, safe and appropriate provision of medical genetics services to the New Zealand public. The report noted the lack of a single agency taking an overarching view of genetic technologies and service delivery, an absence that has implications for the effective regulation of quality assurance in relation to genetic testing [[38], p4]. Echoing some of the findings in the Sarfati report, the NHC report highlighted the lack of a coordinated mechanism for developing and evaluating new tests, the exclusion of genetic tests from the Laboratory Services Schedule and the absence of an organisation responsible for making public funding decisions about these tests. It commented on the risks raised by the increasing availability of tests where utility and validity were uncertain or had been inadequately assessed, and suggested these risks were associated with the death of measures to ensure the quality of new tests [[38], p13]. Problems with quality assurance mechanisms for laboratories were also identified. It found that laboratories carrying out low-volume tests might not be performing tests often enough to maintain competency. Further, as research laboratories need not be IANZ accredited, yet sometimes perform clinical testing services, they may not be subject to adequate quality assurance programmes. The NHC considered that genetic testing particularly challenged the current system of quality assurance, due to its rapid rate of development which demanded more frequent reviews of laboratory competency than presently in place [[38], p18]. Finally, the NHC Report noted that New Zealand needed to consider the particular cultural concerns of the Maori community in developing more effective quality assurance measures. Genetic testing raises two potential concerns for Maori. First, some Maori believe that genetic technology may change the *whakapapa*, a spiritual value that relates to Maori identity and which refers to genealogy, tribal histories and genetic inheritance. Second, that for some Maori it may be culturally inappropriate to send genetic samples outside New Zealand for testing [[38], p23].

The report's major recommendations specifically relevant to quality assurance and genetic testing were that:

• An assessment be made for the applicability of the NHC's New Health Intervention Assessment (NHIA) framework to

the assessment of genetic technologies and genetic tests;

• Clinical validity and utility should direct the funding of new genetic tests;

• The peer review process for genetic testing laboratory accreditation be increased from four to two years to accommodate rapid changes in technology;

• IANZ should accredit laboratories according to professional standards, such as those developed by the Human Genetics Society of Australasia; and

• Protocols should be developed for each test approved for use that cover, among other things, consent protocols, when and how the test should be used and sensitivity to cultural issues (particularly those of the Maori community) [[38], p7].

Overview of Australian and New Zealand reviews

Not surprisingly, given the similarities in their regulatory structures, the Australian and New Zealand reviews identified similar problems in many areas. Two major areas of similarly were that some laboratories providing clinical testing are not required to be accredited; and that there is no effective system in place for ensuring compliance with accreditation standards. A general theme in the reviews was therefore the need to strengthen compliance mechanisms. Finally, the lack of an oversight body for genetic testing was identified as a problem in both New Zealand and Australia. The ALRC recommended the establishment of such a body, and its report provided a detailed account of how this might be achieved and what functions the proposed HGCA should have. New Zealand could draw on this recommendation in establishing a similar body. Alternatively there may be value in Australia and New Zealand examining the option of developing a joint oversight body to advise on issues specific to genetic testing. In other areas, the reviews differed in their focus. One example is the ALRC Inquiry view that measures should be put in place to address direct to the public test provision. This concern received relatively little attention in the New Zealand reports, although it may well be a problem in the New Zealand context as well.

Conclusion

Quality assurance is an important aspect of ensuring patient safety and well-being in relation to genetic testing. The reviews conducted of the Australian and New Zealand schemes to promote quality assurance in genetic testing, in general conclude that these schemes are working well. Both countries have taken a proactive stance in recognizing the need to continually monitor and evaluate their regulatory frameworks and investigate measures to improve them. Since these reviews have been conducted, governments in both countries have taken steps to address the problems identified. Given the rapid advances in the field of genetic testing, we watch with interest as these governments continue to develop their regulatory systems governing quality assurance of genetic tests to ensure patient safety and wellbeing.

Competing interests

Imogen Goold was employed as a Legal Officer by the Australian Law Reform Commission from April 2002 to September 2004 and was involved in researching and writing sections of *Essentially Yours: The Protection of Human Genetic Information in Australia*. The remaining author(s) declare that they have no competing interests.

Authors' contributions

IG carried out reviews of regulations, guidelines and reports, jointly drafted the manuscript and carried out final revisions. AP carried out reviews of regulations, guidelines and reports and jointly drafted the manuscript. SB undertook the initial research and wrote summaries of the research on which the current paper is based, provided feedback on future drafts. AB initiated and oversaw the research, advised on the structure, focus and discussion in the manuscript and provided feedback on drafts. All authors read and approved the final manuscript.

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upon two of the case studies developed as part of this research.

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AUTOIMMUNE HEPATITIS-SPECIFIC ANTIBODIES AGAINST SOLUBLE LIVER ANTIGEN AND LIVER CYTOSOL TYPE 1 IN PATIENTS WITH CHRONIC VIRAL HEPATITIS

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Background: Non-organ specific autoantibodies are highly prevalent in patients with chronic hepatitis C (HCV). Among them, anti-liver kidney microsomal type 1 (LKM1) antibody – the serological marker of type 2 autoimmune hepatitis (AIH-2)- is detected in up to 11% of the HCV-infected subjects. On the other hand, anti-liver cytosol type 1 antibodies (anti-LC1) – either in association with anti-LKM1, or in isolation- and anti-soluble liver antigen antibodies (anti-SLA) have been considered as useful and specific diagnostic markers for AIH. However, their specificity for AIH has been questioned by some recent studies, which have shown the detection of anti-LC1 and anti-SLA by immunoprecipitation assays in HCV patients irrespective of their anti-LKM1 status. The aim of the present study was to test the anti-LC1 and anti-SLA presence by specific enzyme linked immunosorbent assays (ELISAs), in a large group of Greek HCV-infected patients with or without anti-LKM1 reactivity as firstly, immunoprecipitation assays are limited to few specialized laboratories worldwide and cannot be used routinely and secondly, to assess whether application of such tests has any relevance in the context of patients with viral hepatitis since antibody detection based on such ELISAs has not been described in detail in large groups of HCV patients.

Methods: One hundred and thirty eight consecutive HCV patients (120 anti-LKM1 negative and 18 anti-LKM1 positive) were investigated for the presence of anti-LC1 and anti-SLA by commercial ELISAs. A similar number (120) of chronic hepatitis B virus (HBV) infected patients seronegative for anti-LKM1 was also tested as pathological controls.

Results: Six out of 18 (33%) anti-LKMpos/HCVpos patients tested positive for anti-LC1 compared to 1/120 (0.83%) anti- LKMneg/HCVpos patients and 0/120 (0%) of the anti-LKM1neg/HBVpos patients ($p < 0.001$ for both comparisons). Anti-SLA antibodies were not present in any of the HCV (with or without anti-LKM1) or HBV-infected patients.

Conclusion: We showed that anti-LC1 and anti-SLA autoantibodies are not detected by conventional assays in a large group of anti-LKM1 negative patients with chronic hepatitis B and C infections. Based on these results we cannot find any justification for the application of anti-LC1 and anti-SLA tests in the routine laboratory testing of viral hepatitisrelated autoantibody serology with the only potential exception being the anti-LC1 screening in anti-LKM1pos/HCVpos patients.

Background

Non-organ specific autoantibodies (NOSA), particularly smooth muscle antibodies (SMA) and antinuclear (ANA) antibodies are highly prevalent in patients with chronic hepatitis C virus (HCV) infection [1-7]. Anti-liver kidney microsomal type 1 (LKM1) antibody – the serological marker of type 2 autoimmune hepatitis (AIH-2)- is also detected in up to 11% of the HCV-infected subjects [1,8-11]. Anti-liver cytosol type 1 (LC1) antibodies have originally been described either in association with anti-LKM1, or in isolation, and in both instances define a clinical entity indistinguishable from AIH-2 [12,13]. Anti-LC1 has also been found occasionally in anti-LKM1 positive chronic hepatitis C virus (HCV) infected patients [10,14]. Detection of anti-soluble liver antigen antibodies (anti- SLA) was initially considered to identify a third type of AIH seronegative for the conventional ANA, SMA, anti- LKM1 autoantibodies [15] but recent studies indicate that

it can also be present in conjunction with other AIH-specific antibodies suggesting that anti-SLA is rather an additional important marker for the diagnosis of type 1 AIH, than a marker of a third type of AIH [11,16-19]. Hence, anti-LC1 and anti-SLA autoantibodies appear useful diagnostic markers for AIH but their accurate detection was until recently hampered by the fact that anti-LC1 is obscured by the concurrent presence of anti-LKM1 using the indirect immunofluorescence (IIFL) routine screening, while anti-SLA are undetectable by IIFL [9-11]. In recent years, the molecular targets of anti-LC1 and anti- SLA have been identified as formiminotransferase cyclodeaminase (FTCD) and UGA tRNA suppressor associated antigenic protein (tRNP(Ser)Sec), respectively and commercial enzyme linked immunosorbent assay (ELISA) kits for their detection have become available [9,20-25]. Their specificity for AIH, however, has been questioned by studies from the group of Alvarez [26,27]. By immunoprecipitation of radiolabeled human FTCD, Beland et al have found that anti-FTCD antibodies are present in 10% of anti-LKM1 positive and 15% of anti-LKM1 negative chronic HCV infected patients [26]. Of interest and using a similar approach, the same group has detected anti-SLA antibodies in 28% of anti-LKM1 positive and in 12% of anti-LKM1 negative HCV infected patients [27]. These findings challenge the prevailing notion that antibodies against human FTCD and tRNP(Ser)Sec are highly specific for autoimmune liver diseases [20-25,28,29]. According to the authors of the abovementioned studies [26,27], anti-LC1 and anti-SLA autoantibodies can be regarded as serological markers of autoimmunity and need to be tested when investigating autoimmunity, especially in chronic HCV infection. Immunoprecipitation assays, however, are limited to few specialized laboratories worldwide and cannot be used routinely. Indeed, most of the non-specialized laboratories have started making use of kit-based semi-automated commercial anti-LC1 and anti-SLA ELISAs. The question as to whether application of such tests has any relevance in the context of patients with viral hepatitis still remains unanswered, as antibody detection based on such ELISAs has not been described in detail in large groups of patients with chronic viral hepatitis B and C. The aim of the present study was to test anti-FTCD (anti- LC1) and anti-tRNP(Ser)Sec (anti-SLA) antibodies, in a large number of Greek HCV-infected patients with or without anti-LKM1 seropositivity. A similar number of chronic hepatitis B virus (HBV) infected patients was also tested as pathological controls. We were able to show that there is no reason for additional routine laboratory testing for anti-LC1 and anti-SLA antibodies in HCV-infected patients unless there are anti-LKM1 antibodies present.

Methods

Patients

One hundred and twenty consecutive patients with chronic hepatitis C (mean age 47 ± 12.3 standard deviation (SD) years; 62 female), seronegative for anti-LKM1 (anti-LKMneg/HCVpos) by IIFL followed at the Department of Medicine, Academic Liver Unit, University of Thessaly Medical School were studied. The diagnosis of chronic HCV infection was based on: (a) detection of anti-HCV antibodies using a third-generation ELISA (Murex Diagnostics, Temple Hill, Dartford, UK) at least twice within 6 months before their enrolment into the study; and (b) active virus replication as defined by the detection of HCV RNA using a commercially available qualitative PCR kit (HCV Monitoring Cobas Amplicor, Roche, Geneva, Switzerland), as described previously [1,2,30]. At the time of serum sample collection, 45 patients had completed antiviral treatment with alpha-interferon (IFN-a) alone or in combination with ribavirin. All patients were negative for the following viral markers tested using commercial kits (Abbott Diagnostic Kits, North Chicago, IL, USA): Hepatitis B surface Antigen (HBsAg), anti-HBsAg antibody (anti- HBs), anti-Hepatitis B core antibody (anti-HBc), and antihuman immunodeficiency virus (anti-HIV, VIDAS HIVDUO Bio MER©IEUX, Marcy-l'Etoile, France). Histological, serological and clinical details of these patients have been described in previous reports [1,2,30]. The results obtained by ELISA testing of the anti-LKM1 negative patients with hepatitis C were compared to those obtained by testing of 18 anti-LKM1pos/HCVpos patients (mean age 47 ±

11.3 years; 12 female) and 120 anti-LKM1neg/HBVpos Greek patients (mean age 49.1 ± 11.2; 81 male) all HBV-DNA positive by a sensitive PCR kit (HBV Monitor Cobas Amplicor, Roche; cut-off: 200 copies/ml) and negative for HCV markers.

Autoantibody detection

Presence of ANA, SMA, anti-LKM1, anti-LC1 and antimitochondrial antibodies was initially detected by IIFL on 5 • m frozen sections of in-house rodent multi-organ (kidney, liver and stomach) tissue substrates using as revealing reagent an anti-total human IgG fluorescein isothiocyanate conjugate (Dako Ltd, High Wycombe, Bucks, UK), as previously described [1,9]. Briefly, diluted sera (1/40) in phosphate buffered saline (PBS) were tested on inhouse snap-frozen sections of rat liver, kidney and stomach. Positive sera were titred by double dilution to extinction. The patterns of reactivity were assessed under a fluorescence microscope (Orthoplan, Leitz, Wetzlar, Germany). Anti-LKM1, anti-LC1 and anti-SLA reactivity was also evaluated by Western immunoblotting using both human microsomal and cytosolic fraction as antigen sources (Euroimmun, Lübeck, Germany). Commercially available ELISA (Euroimmun) were used for the detection of anti-FTCD (anti-LC1) and tRNP(Ser)Sec (anti-SLA) autoantibodies, according to the manufacturer's instructions. Antibody binding titres expressed as optical density (OD) testserum/OD calibrator and extinction values of serum samples exceeding those of the calibrator (OD testserum/OD calibrator > 1) were considered positive.

Inhibition studies

To investigate whether the 58–60 kDa band immunofixed by anti-LC1 is FTCD, inhibition experiments were performed using the anti-LC1 positive serum, diluted at 1/ 200, and pre-incubated with solid phase recombinant FTCD (Euroimmun), as previously described [31,32]. Each patient gave informed consent to participate in this study. The Local Ethical Committee of The Medical School, University of Thessaly approved the study protocol.

Statistical analysis

Data are presented as percentages (%) or mean ± SD unless otherwise stated. The differences between different groups were compared using t-test, the Mann Whitney U test, • 2, (two by two with Yates' correction) and Fisher's exact test as appropriate. Two-sided *p* values < 0.05 were considered as statistically significant.

Results and discussion

Prevalence of various NOSA is summarised in Table 1. Anti-FTCD (anti-LC1) antibodies were present in 6/18 (33%) anti-LKMpos/HCVpos compared to 1/120 (0.83%) anti-LKMneg/HCVpos patients (a 47-years old male patient at the third month of IFN-a treatment with no evidence of aminotransferases flare and without history of extrahepatic immunopathological manifestations) and 0/120 (0%) of the anti-LKM1neg/HBVpos patients (p < 0.001 for both; Figure 1A). By western blot using a human liver cytosolic fraction as substrate, the anti-FTCD positive anti-LKMneg/HCVpos case immunofixed a relatively weak 58– 60 kDa band corresponding to LC1 autoantigen (Figure 2, lane 1). This band was almost completely abolished when the reactive serum was pre-incubated with recombinant FTCD as solid phase competitor (Figure 2, lane 2) indicating that is due to anti-FTCD reactivity. Repeat IIFL of this case revealed absence of a pattern typical of anti-LC1; there was no staining of cytoplasm of liver cells with relative sparing of the centrilobular area, even when the serum was tested at dilution of 1/20. Anti-tRNP(Ser)Sec (anti-SLA) antibodies were not present in any of the HCV (with or without anti-LKM1 reactivity) or HBV infected patients (Figure 1B). Similar data we have obtained when an anti-SLA ELISA of another manufacturer (Inova Diagnostics, San Diego, California, USA) was used (data not shown). Chronic HCV infection is frequently characterized by an altered immune homeostasis as it has become evident by the high prevalence of NOSA, and in particular SMA and ANA which, according to some reports, exceeds 50% of the infected population [1-7]. Anti-LKM1 antibody – the serological marker of type 2 AIH- is also detected in up to 11% of the HCV-infected subjects [1,8-11]. Under this context, the detection of anti-LC1 and anti-SLA antibodies in a significant proportion of HCV patients in the two recent studies – irrespective of the anti-LKM1 status –

Table 1: Prevalence of non-organ specific autoantibodies detected by indirect immunofluorescence (IIFL) or enzyme linked immunosorbent assay (ELISA) in patients with chronic hepatitis C and B.

	Anti-LKM1 (IIFL)	Anti-LC1 (ELISA)	Anti-SLA (ELISA)	ANA (IIFL)	SMA (IIFL)
LKM1^{pos}/HCV^{pos}	18/18 (100%)*	6/18 (33%)	0/18 (0%)	5/18 (27.7%)**	6/18 (33%)***
LKM1^{neg}/HCV^{pos}	0/120 (0%)	1/120 (0.8%)	0/120 (0%)	45/120 (37.5%)**	61/120 (50.8%)***
LKM1^{neg}/HBV^{pos}	0/120 (0%)	0/120 (0%)	0/120 (0%)	23/120 (19.2%)**	15/120 (12.5%)***

LKM1, liver kidney microsomal type 1; LC1, liver cytosol type 1; SLA, soluble liver antigen; ANA, anti-nuclear antibody; SMA, smooth muscle antibody; pos, positive; neg, negative; *Confirmed by Western immunoblotting (see Methods section); **Low titers of ANA were detected in the three groups (mean titer: 1/168, 1/148 and 1/140, respectively); ***Low titers of SMA were detected in the three groups (mean titer: 1/134, 1/121 and 1/119, respectively).

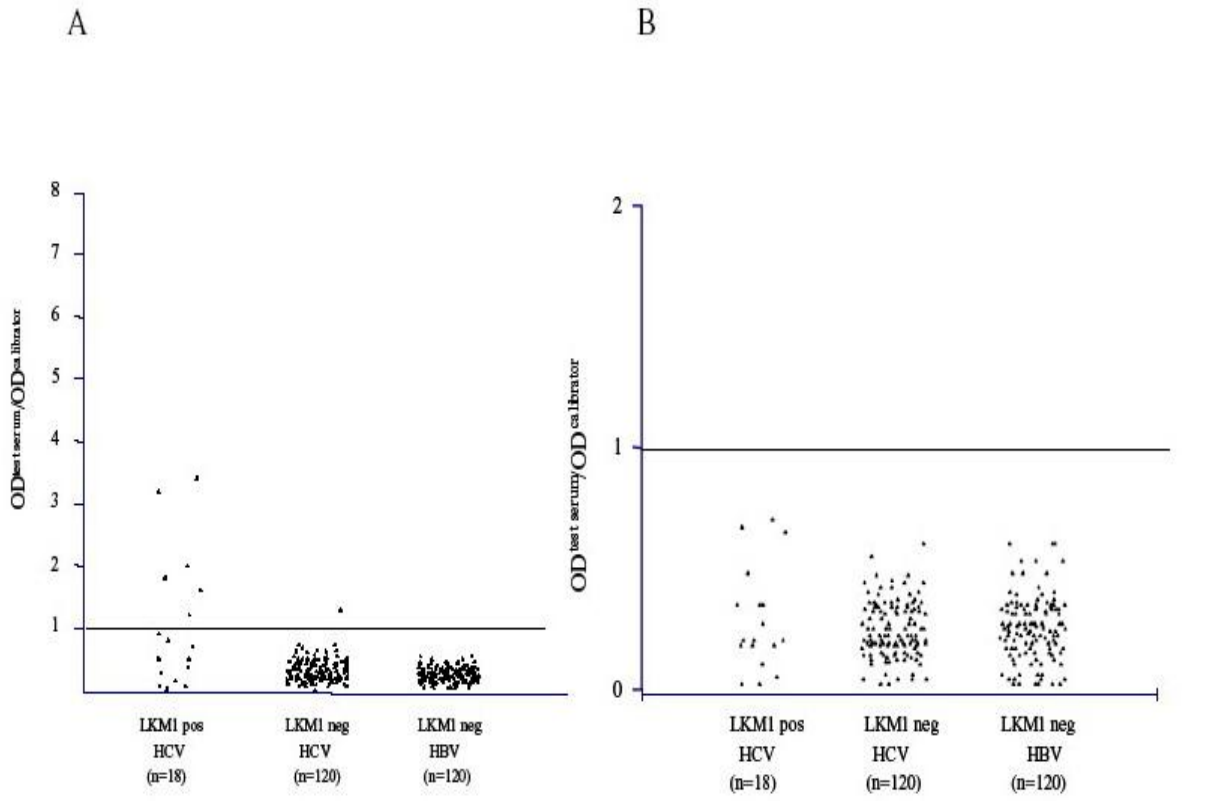

Figure 1
(A). ELISA titers of anti-formimino-transferase cyclodeaminase (anti-FTCD) antibodies, known also as anti-liver cytosolic type 1 antibodies (anti-LC1) and (B). titers of anti-UGA tRNA suppressor associated antigenic protein (tRNP(Ser)Sec) antibodies, known also as anti-soluble liver antigen antibodies (anti-SLA) in 18 liver kidney microsomal type 1 (LKM1) positive chronic hepatitis C virus (HCV) infected patients; 120 LKM1 negative chronic HCV infected patients; and 120 LKM1 negative hepatitis B virus (HBV) infected patients. According to the manufacturer's instructions, autoantibody reactivity is considered positive when optical density (OD)test serum/ODcalibrator > 1.

[26,27] could not be a surprising finding as it might further support the autoimmune propensity of the virus. The findings of the present study however, suggest that commercially available assays are unable to detect anti- LC1 and anti-SLA antibodies in a

large number of anti- LKM1 negative patients either with chronic HCV or with chronic HBV infection. On the contrary, we found that a considerable proportion of anti-LKMpos/HCVpos patients (33%) had detectable anti-LC1 antibodies by ELISA, which is in accordance with previous studies from Italy [14]. The question arises as to whether the inability of the detection of anti-LC1 and anti-SLA antibodies by ELISAs in patients with chronic HCV infection is due to the superior sensitivity of the immunoprecipitation assays used by Beland et al [26] and Vitozzi et al [27]. Radioligand assays of higher sensitivity than the conventional assays have increasingly been reported in the autoantibody diagnostic setting of a plethora of autoimmune diseases such as diabetes, multiple sclerosis, systemic lupus erythematosus and AIH [1,28,33-38]. There are still some reservations however, as to whether this is the sole reason for the discrepant results between ELISAs and immunoprecipitation assays specific for anti-LC1 and anti-SLA detection. First, it has been generally agreed that as equipment becomes more sophisticated, higher diagnostic sensitivity of an assay frequently comes at the expense of a lower specificity [38]. Beland et al [26] and Vitozzi et al [27] argue that this cannot be the case for their immunoprecipitation anti-LC1 and anti-SLA assays because they can detect these autoantibodies in patients with chronic hepatitis C but not in other pathological controls. These investigators, in particular, were unable to detect anti-LC1 in any of the 22 patients with type 1 AIH or the 25 patients with other unrelated chronic liver diseases (which however did not describe in detail). The focus of the present study was not the validation of the findings of the French/Canadian group. We rather decided to investigate the prevalence of anti-LC1 and anti- SLA in anti-LKM1neg/HCVpos patients by commercial ELISAs and to test their diagnostic utility in the day-to-day clinical practice. Our assumption has been based on the fact that if anti-LC1 and anti-SLA are present in anti- LKM1neg/HCVpos patients and these antibodies can be detected by routinely performed ELISAs, clinicians should be aware and request for their detection. We have found that neither anti-LC1 nor anti-SLA autoantibodies are detectable in anti-LKM1 negative patients with chronic viral hepatitis C or B by ELISAs.

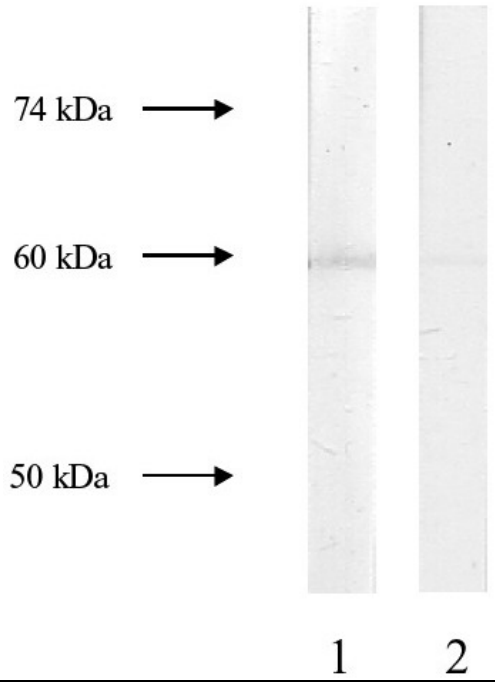

Figure 2
Immunoblot pattern produced by a serum sample from a liver kidney microsomal type 1 (LKM1) negative chronic hepatitis C virus (HCV) infected patient with anti-formiminotransferase cyclodeaminase (FTCD) antibodies on electrophoretically separated human liver homogenate (lane 1). The 58–60 kDa immunofixed band almost completely abolished when the reactive serum was pre-incubated with recombinant FTCD as solid phase competitor (lane 2).

Conclusion

We showed that anti-LC1 and anti-SLA autoantibodies are not detected by conventional assays in he vast majority of patients with chronic viral hepatitis B and C. Based on these results we cannot find any justification for the application of anti-LC1 and anti-SLA tests in the routine laboratory testing of viral hepatitis-related autoantibody serology unless anti-LKM1 antibodies are present in HCVinfected patients. In the latter case, only anti-LC1 screening could be of interest. Exchange of sera and standardization of the methodology employed, whether it is radioligand, western blot or ELISA

is urgently warranted to address definitely whether anti-LC1 and anti-SLA autoantibodies are serological markers of chronic hepatitis C.

Abbreviations

AIH, autoimmune hepatitis; SMA, smooth muscle antibody; ANA, antinuclear antibody; anti-LKM1, liver kidney microsomal type 1 antibody; IIFL, indirect immunofluorescence; anti-LC1, liver cytosol type 1 antibody; anti-SLA, antibody against soluble liver antigen; HCV, hepatitis C virus; HBV, hepatitis B virus; FTCD, formiminotransferase cyclodeaminase; tRNP(Ser)Sec, UGA tRNA suppressor associated antigenic protein; ELISA, enzyme linked immunosorbent assay; IFN-a, alpha-interferon.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

EIR and GND had the original idea for the study and wrote the paper; MM, OR and CL carried out the autoantibodies serological tests as well as the inhibition experiments and along with ER performed the statistical analysis; EIR and GND contributed to the final version of the article. All authors have read and approved the final version of the manuscript.

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EVALUATION OF ANTIBODIES AGAINST HUMAN HSP60 IN PATIENTS WITH MPO-ANCA ASSOCIATED GLOMERULONEPHRITIS: A COHORT STUDY

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Background: Human Heat Shock Protein 60 (hHSP60) has been implicated in autoimmunity through molecular mimicry, based on the high degree of homology with HSP65 of micro-organisms leading to autoimmune recognition of the human protein. Additionally, sequence homology between hHSP60 and myeloperoxidase (MPO) has been described. MPO is a major autoantigen in vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA). We hypothesized that infections may trigger the ANCA response against MPO through hHSP60.
Methods: In 86 consecutive patients with ANCA-associated vasculitis (AAV), anti-hHSP60 and anti-mycobacterial HSP65 were measured by ELISA. Patients were compared with 69 healthy controls (HC). Continuous data between groups were compared using Wilcoxon signed rank test and Kruskal-Wallis test with Dunn's post-test when appropriate. Correlations between data were derived using Spearman correlation. Odds ratios and 95% confidence intervals were obtained using Fisher's exact test.
Results: At diagnosis, median anti-mHSP65 level was higher in AAV (median [range]: 42.5 [0–500]), and subsequently in MPO-ANCA (44 [7–500]), compared to HC (22 [0–430]). Anti-hHSP60 levels in AAV were not higher compared to HC (18 [0–319] and 18.5 [0–98], respectively). However, in MPO-ANCA anti-hHSP60 levels were increased (32.5 [0–319]) compared to PR3- ANCA (13 [0–79]) and HC. We could not detect cross-reactivity between hHSP60 and MPOANCA. There was a correlation between anti-mHSP65 and anti-hHSP60 levels (r = 0.32, *P* = 0.003) but not between anti-hHSP60 and MPO-ANCA (r = -0.064, *P* = 0.69).
Conclusion: Antibodies against mHSP65 are higher in AAV compared to HC, and anti-hHSP60 antibodies are higher in patients with MPO-ANCA than in patients with PR3-ANCA and HC. Although this finding may be indicative for cross-reactivity between MPO-ANCA and hHSP60, additional assays did not support this hypothesis.

Table 1: Demographic data on patients and healthy controls

	AAV (*N* = 86)	MPO-ANCA (*N* = 42)	PR3-ANCA (*N* = 44)	HC (*N* = 69)
Age (years)*	62.2 ± 13.5	65.9 ± 10.9	59.7 ± 15.2	40.4 ± 9.8
Male gender (%)	69	64	73	59

AAV, ANCA-associated vasculitis; MPO-ANCA, antineutrophil cytoplasmic antibodies against myeloperoxidase; PR3-ANCA, ANCA against proteinase 3; HC, healthy controls
* Mean ± standard deviation

Introduction

Small vessel vasculitides, such as Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA), are strongly associated with antineutrophil cytoplasmic antibodies (ANCA), which are either directed to myeloperoxidase (MPO) or proteinase 3 (PR3) [1-3]. These diseases can occur in any organ system but the respiratory tract and the kidneys are most frequently involved. Untreated, WG results in death within weeks to months. Since the introduction of cyclophosphamide and prednisolone as standard treatment, survival has improved dramatically from less than 20% at 1

year reported in 1958 [4] to at least 60% 5-years survival reported in the past ten years [5-8]. The mechanism by which ANCA are induced is as yet unclear. Certain drugs have been linked to the induction of ANCA and the onset of ANCA-associated vasculitis (AAV) [9]. Recently, it has been described that an autoimmune response may be induced by the presence of a peptide that is antisense or complementary to the autoantigen, for instance, PR3 [10]. This immune response may induce anti-idiotypic antibodies (autoantibodies) that cross-react with the autoantigen. Another favored hypothesis is that infections may trigger an ANCA response [11]. The proposed mechanisms by which infections break self tolerance can include bystander damage, unveiling of 'hidden' self epitopes, determinant molecular spreading and molecular mimicry [11]. Heat Shock Protein (HSP) 65 is an immunodominant antigen in micro-organisms, and has already been implicated in the pathogenesis of vasculitides such as Kawasaki disease [12] and Behcet disease [13]. The human equivalent, hHSP60, has been implicated in autoimmunity through molecular mimicry, based on the high degree of homology with HSP65 of micro-organisms leading to autoimmune recognition of the human protein [14]. In its turn, HSP60 shares sequence homology with MPO [15]. Thus, infections may trigger the ANCA response against MPO through hHSP60. To test this hypothesis, we determined the presence of antibodies against hHSP60 and mycobacterial HSP65 (mHSP65) in patients with MPOANCA and compared them to patients with PR3-ANCA and healthy controls (HC). Results showed that antibodies against mHSP65 are higher in AAV compared to HC, and anti-hHSP60 antibodies are higher in patients with MPO-ANCA than in patients with PR3-ANCA and HC. However, additional assays did not support our hypothesis of cross-reactivity between MPO-ANCA and hHSP60.

Methods

Patients

We retrospectively identified all patients in our renal biopsy registry [16,17] diagnosed with crescentic glomerulonephritis between January 1977 and July 2003 without evidence of systemic lupus erythematosus, IgA nephropathy, Henoch Schönlein purpura, post-infectious glomerulonephritis or cryoglobulinaemia. Serum samples, taken at the time of biopsy, were tested for the presence of ANCA, according to a multistep procedure that combines indirect immunofluorescence with direct and capture enzyme-linked immunosorbent assays (ELISAs) [18]. We thus identified 109 patients with AAV with biopsy-proven renal involvement: 46 patients with PR3-ANCA only (42%), 49 patients with MPO-ANCA only (45%), 4 patients with both PR3- and MPO-ANCA (4%) and 10 patients with MPO-ANCA with the presence of antiglomerular basement membrane antibodies (9%). Only patients who were single positive for PR3- or MPO-ANCA, and had enough serum available for all tests, were included (n = 86). Additionally, 40 healthy controls (HC) (laboratory personnel) were tested to determine the cutoff value for the anti-hHSP60 test and, 69 HC were tested to determine the cut-off value for the anti-mHSP65 test. This study was performed in accordance with the 1997 Declaration of Helsinki of the World Medical Association. Demographic data on patients and controls are presented in table 1.

Sera

Serum samples, taken at the time of biopsy, were used to determine the presence of anti-hHSP60 and anti-mHSP65 in patients with AAV. These sera had been stored at -80°C, in some patients for over 20 years. However, when testing the antibody response, there was no difference in antibody level between patients included in 2003 and patients included in earlier years.

ELISA for the detection of antibodies against human

HSP60 and mycobacterial HSP65

Recombinant hHSP60 (Stressgen, Victoria, Canada) was diluted to 2 µg/mL in coating buffer containing 0.1 M NaHCO3 - (pH 9.6), and 50 µL/well (i.e., 0.1 µg/well) was incubated in wells of microplates (Nunc MaxiSorp™, Rochester, NY) overnight at 4°C. Control wells were incubated with coating buffer alone. Wells were then incubated overnight at 4°C with 100 µL/well coating buffer containing 1% grade V bovine serum albumin (BSA, Sigma, St. Louis, MO) to block

non-specific binding. Plates were then washed 3 times with PBS containing 0.05% Tween 20 (PBS-T). Plates were preincubated at room temperature with 200 µL/well of preincubation buffer, containing 0.05% Tween 20 and 1% BSA in PBS, for 1 hour. After washing 2 times with PBS-T, wells were incubated in triplicates with patient serum in a previously established optimal dilution of 1:50, 50 µL/well, in incubation buffer and kept overnight at 4°C. The next day, plates were washed 5 times with PBS-T and incubated with goat F(ab')2 anti-human IgG (Fc)-horseradish peroxidase conjugate (Cappel-ICN Immunobiologicals, Costa Mesa, CA), diluted 1:2000 in incubation buffer, for 2 hours at room temperature. After washing 5 times with PBS-T, 100 µL of freshly made substrate (containing 0.5 mg/mL o-Phenylenediamine (Sigma) and 0.03% H2O2 in citrate/phosphate buffer, pH 4.9) was added to each well. After 10 minutes, the reaction was stopped with 50 µL 4N H2SO4 and absorbances were read at 490 nm. Results are expressed as anti-hHSP60 levels in arbitrary units (AU)/ mL. Hereto, the mean OD of the triplicates was corrected for non-specific binding by subtraction of the mean OD in uncoated wells. Next, a standard curve was created by including in every assay a serial, 2-step dilution from 1:10 to 1:640 of a positive serum sample with anti-hHSP60 reactivity. The undiluted serum sample was arbitrarily assigned 100 AU/mL. Additionally, results are expressed as positive or negative. To establish the cut-off value for this test, the mean AU/mL and SD of the sera of 40 HC were determined, and the cut-off value was set at the mean + 2 SD. For detection of antibodies against mHSP65, essentially the same procedure was followed. Recombinant mHSP65 (Stressgen) was diluted to 2 µg/mL and coated in a concentration of 0.1 µg/well. Serum was diluted 1:50 prior to incubation. To read results in AU, a standard curve was created as described for anti-hHSP60 antibodies. To establish the cut-off value for this test, the mean AU/mL and SD of the sera of 69 HC were determined, and the cut-off value was set at the mean + 2 SD.

Myeloperoxidase inhibition assays

To test cross-reactivity between MPO and hHSP60, serum from one patient being positive for both MPO-ANCA and anti-hHSP60 antibodies was incubated for 30 minutes at 37°C with MPO or hHSP60 in concentrations of 1, 3, 10 and 20 µg/mL. The serum was then tested in the antihHSP60 ELISA as described above, or in the MPO-ANCA ELISA using commercially available direct ELISA kits (Euro-diagnostica, Malmö, Sweden). Additionally, absorption tests were performed in which ELISA plates were coated with hHSP60 or MPO and incubated with serum. The next day, or the second day, anti-hHSP60 reactivity in this pre-absorbed serum was tested as described above for the anti-hHSP60 ELISA. Unfortunately, this was the only patient of whom enough serum was present to perform the described tests.

Statistical analyses

All data are presented as median [range] unless stated otherwise. Continuous data between groups were compared using Wilcoxon signed rank test and Kruskal-Wallis test with Dunn's post-test when appropriate. Due to the perceived relevance of the results, we did not only perform Dunn's post-test for subgroup analysis, but we also compared subgroups using Wilcoxon signed rank test. Correlations between data were derived using Spearman correlation. Odds ratios (OR) and 95% confidence intervals (CI) were obtained using Fisher's exact test. Analyses were performed with GraphPad Prism version 3.00 and GraphPad Instat software package version 2.04a (both GraphPad Software Inc., San Diego, CA). A two-sided pvalue < 0.05 was considered to indicate statistical significance.

Results

Eighty-six consecutive patients with AAV (44 PR3- and 42 MPO-ANCA) were included in the study. Mean age was 62.2 ± standard deviation 13.5 (65.9 ± 10.9 in MPOANCA and 59.7 ± 15.2 in PR3-ANCA, $P = 0.07$). Fifty-nine patients (69%) were male (27 patients (64%) in MPOANCA and 32 patients (73%) in PR3-ANCA, $P = 0.49$).

Anti-mycobacterial HSP65 antibodies are elevated in

MPO-ANCA compared to healthy controls

In patients with AAV, median anti-mHSP65 level was 42.5 AU/mL [0–500], compared to 22 AU/mL [0–430] in healthy

controls (P = 0.008, figure 1). In MPO-ANCA, antibody levels were significantly higher (44 AU [7–500]) compared to HC (P = 0.006, figure 1). In patients with PR3-ANCA, there was a trend to a higher antibody level (42.5 AU [0–500] compared to HC (P = 0.10). With a cutoff value of 88.5 AU/mL, 13 of 69 HC (19%) were positive for anti-mHSP65 compared to 23 of 86 (27%) patients with AAV (P = NS). Eleven of 44 (25%) patients with PR3- ANCA were positive for anti-mHSP65 compared to 12 of 42 patients with MPO-ANCA (29%) (P = NS). Next, we confirmed the specificity of the anti-mHSP65 antibodies by immunoblotting. To this end we selected 5 sera that were positive by ELISA. All sera reacted with a 65 kD band in an immunoblot with recombinant mHSP65 (data not shown).

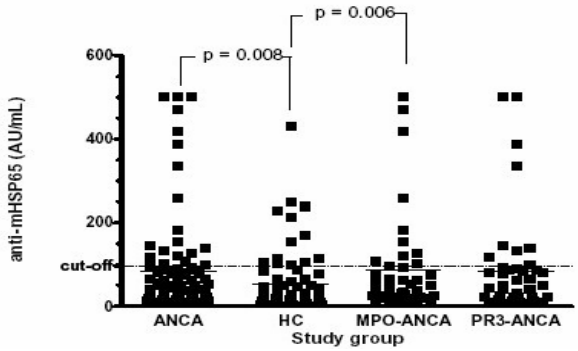

Figure 1
Anti-mHSP65 antibody levels in healthy controls (HC) and in patients with ANCA-associated vasculitis (AAV). Anti-mycobacterial Heat Shock Protein 65 (anti-mHSP65) antibody levels are significantly higher in AAV compared to HC (42.5 AU/ mL [0–500] and 22 AU [0–430], respectively). Furthermore, anti-mHSP65 antibody levels in patients with PR3- and MPOANCA are shown. Anti-mHSP65 is comparable between patients with MPO-ANCA and PR3-ANCA (44 AU [7–500], and 42.5 AU [0–500], respectively). In patients with MPOANCA, anti-mHSP65 antibody level is significantly higher when compared to HC (P = 0.006). Dotted line represents cut-off value; solid line represents median value.

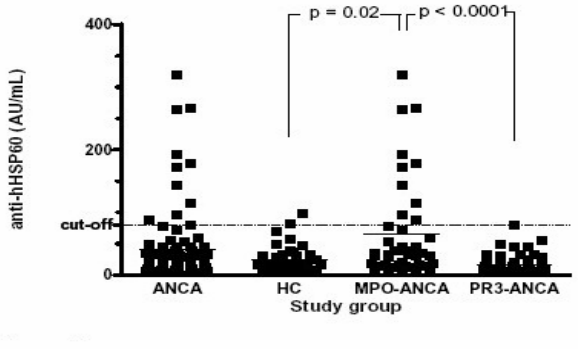

Figure 2
Anti-hHSP60 antibody levels in healthy controls (HC) and in patients with ANCA-associated vasculitis (AAV). Anti-human Heat Shock Protein 60 (anti-hHSP60) antibody levels are not significantly higher in AAV compared to HC (18 AU/mL [0– 319] and 18.5 AU [0–98], respectively). Furthermore, antihHSP60 antibody levels in patients with PR3- and MPOANCA. Anti-hHSP60 are significantly higher in patients with MPO-ANCA compared to PR3-ANCA (32.5 AU [0–319], and 13 AU [0–79], respectively). In patients with MPOANCA, anti-hHSP60 antibody level is also significantly higher when compared to HC (P = 0.02), whereas in PR3-ANCA, it is not. Dotted line represents cut-off value; solid line represents median value.

Anti-human HSP60 antibodies are elevated in MPO-ANCA compared to PR3-ANCA and healthy controls

In patients with AAV, median anti-hHSP60 level was 18 AU/mL [0–319], compared to 18.5 AU/mL [0–98] in healthy controls (P = NS, figure 2). In MPO-ANCA, antibody levels were significantly higher (32.5 AU [0–319]) compared to HC (P = 0.02) and PR3-ANCA (13 AU [0– 79]) (P < 0.0001, figure 2). Patients with PR3-ANCA did not have higher antibody levels than HC. With a cut-off value of 80 AU/mL, 2 of 40 HC (5%) were positive for anti-hHSP60 compared to 12 of 86 (14%) patients with AAV (P = NS). One of 44 (2.3%) patients with PR3-ANCA was positive for anti-hHSP60 compared to 11 of 42 patients with MPO-ANCA (26%) (P = 0.001, OR 15.3, 95% CI 1.9 – 124). Next, we confirmed the specificity of the anti-hHSP60 antibodies by immunoblotting. To this end we selected 5 sera that were positive by ELISA. All sera reacted with a 60 kD band in an immunoblot with recombinant hHSP60 as well as with native bovine HSP60. The latter indicates that the antigenicity of recombinant and native HSP60 compares well (data not shown).

Myeloperoxidase does not inhibit anti-hHSP60 antibody reactivity

To test whether anti-hHSP60 antibodies actually crossreact with MPO, we performed inhibition assays incubating serum from the patient with the highest anti-hHSP60 response with MPO or hHSP60 and testing for hHSP60 and MPO reactivity. Incubation with increasing concentrations of MPO inhibited the MPO-ANCA response in a dose-dependent manner (figure 3A). However, incubation of serum with hHSP60 did not inhibit the MPOANCA reactivity (figure 3A). Additionally, MPO was unable to inhibit the anti-hHSP60 antibody reactivity (figure 3B). However, incubation with hHSP60 did not inhibit the anti-hHSP60 response (figure 3B). To test for the ability of hHSP60 to inhibit anti-hHSP60 reactivity, absorption tests were performed. Results now showed inhibition of the anti-hHSP60 response by hHSP60 but not by MPO (figure 4).

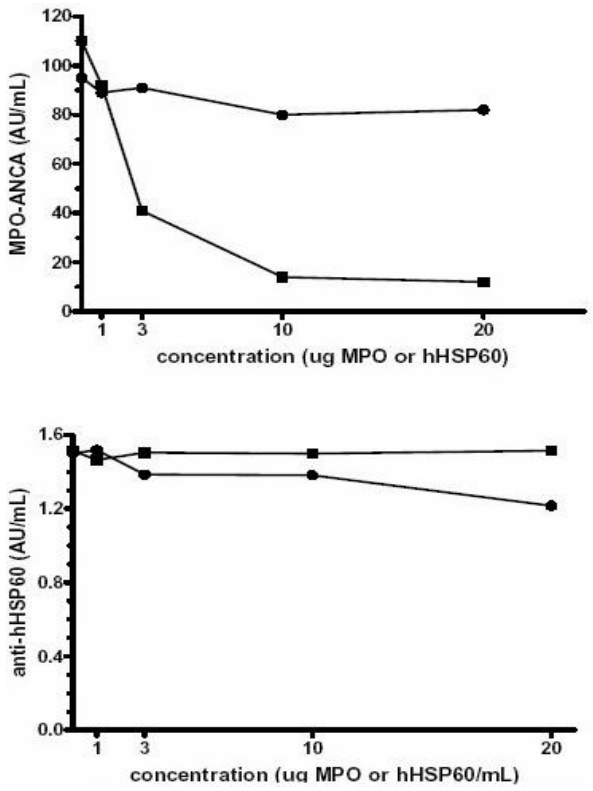

Figure 3

Upper panel: (3A) MPO-ANCA inhibition assay. Incubation with increasing concentrations of myeloperoxidase (MPO) (1 – 20 µg/mL) leads to a reduction in MPO-ANCA reactivity (■). In contrast, incubation with human Heat Shock Protein 60 (hHSP60) (1 – 20 µg/mL) does not decrease MPO-ANCA reactivity (●). Lower panel: (3B) Anti-human Heat Shock Protein 60 (hHSP60) inhibition assay. Incubation with increasing concentrations of myeloperoxidase (MPO) (1 – 20 µg/mL) does not lead to a reduction in anti-hHSP60 reactivity (■). However, incubation with hHSP60 (1 – 20 µg/mL) only slightly decreases anti-hHSP60 reactivity (●)

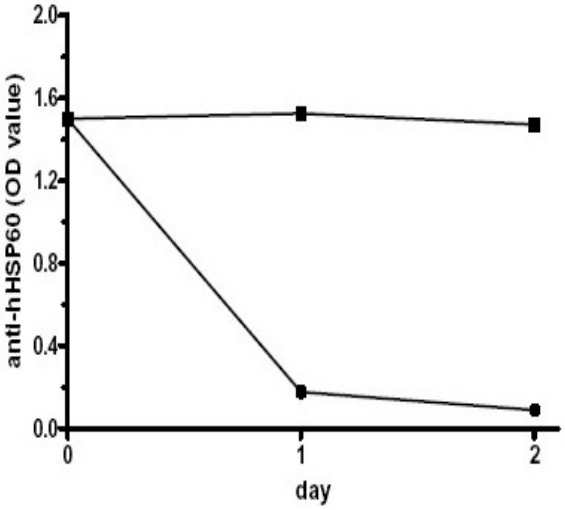

Figure 4

MPO and hHSP60 absorption assays. Incubation of serum in ELISA plates coated with human Heat Shock Protein 60 (hHSP60) for 1 or 2 days leads to a reduction in anti-hHSP60 reactivity (●). In contrast, incubation of serum in ELISA plates coated with myeloperoxidase (MPO) does not decrease anti-hHSP60 reactivity (■).

Follow-up anti-hHSP60 levels

To further exclude cross-reactivity between hHSP60 and MPO-ANCA, we tested whether anti-hHSP60 antibody levels were only present if there was presence of MPOANCA. In the patient with MPO-ANCA and the highest anti-hHSP60 level, follow-up serum samples were availa-ble to test for the presence of anti-hHSP60. As shown in figure 5, anti-hHSP60 levels dropped analogous to MPOANCA levels once treatment has commenced, but slightly increased with tapering of the treatment while MPOANCA levels remained undetectable.

Correlation between anti-mHSP65 and anti-hHSP60 but not between MPO-ANCA and anti-hHSP60 antibodies

Finally, we checked whether correlation exists between antibody levels against mHSP65, hHSP60, and MPO. There was a correlation between height of antibody levels against mHSP65 and hHSP60 (Spearman r = 0.32, *P* = 0.003), but no correlation existed between MPO-ANCA and anti-hHSP60 (Spearman r = -0.064, *P* = 0.69). Also, there was no correlation between anti-mHSP65 and MPO-ANCA (Spearman r = 0.074, *P* = 0.65).

Discussion

The mechanism by which ANCA are induced are as yet unclear. One favored hypothesis is that infections may trigger an ANCA response [11]. We hypothesized that infections may trigger the ANCA response against MPO through hHSP60. We found that anti-hHSP60 was almost exclusively found among patients with MPO-ANCA when compared to PR3-ANCA, supporting our hypothesis. Nevertheless, there was no correlation between MPO-ANCA and anti-hHSP60 antibody levels, and inhibition and absorption assays did not show cross-reactivity between hHSP60 and MPO-ANCA. Furthermore, when we determined the anti-mHSP65 response in AAV and HC, we found no difference between patients with MPO-ANCA and patients with PR3-ANCA, and only a weak correlation between anti-hHSP60 antibody levels and anti-mHSP65 levels. However, not every patient who was positive for anti-hHSP60 had antibodies against mHSP65, suggesting that anti-hHSP60 and anti-mHSP65 are not the same antibodies, and that an anti-hHSP60 response may not be triggered simultaneously with an anti-mHSP65 response. Increased anti-HSP antibody levels, as observed in the present study, might be artificial because of two reasons. First, patients with several systemic autoimmune diseases are known to have increased levels of circulating IgG and this might result in a simultaneous increase in antibodies to, for instance, HSP60 and HSP65. Although analysis of IgG levels is not a standard procedure for the diagnostic work-up of an AAV patient, IgG data were available for a subset of patients included and all were within the normal range (data not shown). Furthermore, to our knowledge such hypergammaglobulinaemia has not been described for AAV. Second, since healthy controls in the current study were of lower age than the AAV patients, increased levels of antibodies to HSP60 and HSP65 might be due to ageing. Again this is not very likely since there was no correlation whatsoever ($R2 < 0.1$) between antibody titers and age (data not shown). Therefore we conclude that antibody levels to HSP60 and HSP65 are really increased in AAV patients as compared to healthy controls. The shared sequence homology described between hHSP60 and MPO is a theoretical one, based on amino acid sequence. This sequence similarity has a length of 17 amino acids and is present on the heavy chain of myeloperoxidase [15]. The sequence is present in a region of myeloperoxidase that is recognized as an epitope by MPO-ANCA in some patients [19]. However, it is unknown whether anti-hHSP60 antibodies bind to the corresponding amino acid sequence of hHSP60. To test whether anti-hHSP60 antibodies actually cross-react with MPO, we performed inhibition assays incubating serum from the patient with the highest anti-hHSP60 response with MPO or hHSP60 and testing for hHSP60 and MPO reactivity. We could not detect a decrease in hHSP60 reactivity when serum was incubated with MPO, suggesting that although sequence homology exists, epitopes recognized by MPO-ANCA are different from those recognized by anti-hHSP60 antibodies. Obviously, this test cannot completely exclude that cross-reactivity exists in other patients, although the absence of correlation between MPO-ANCA and anti-hHSP60 also does not support such cross-reactivity. Antibodies against hHSP60 are associated with the presence and severity of atherosclerosis [20-22], although this has been disputed by others [23]. Interestingly, we found elevated levels of anti-hHSP60 antibodies only in patients with MPO-ANCA. An explanation for this finding may be that diagnosis of MPO-AAV is often delayed, and this may lead to prolonged inflammation and eventually to elevated levels of anti-hHSP60 in MPO-ANCA patients when compared to PR3-ANCA patients. Our data might indicate that cardiovascular disease is more often present in patients with MPO-ANCA. However, follow-up data in our small study do not confirm this.

Interestingly, anti-hHSP60 reactivity could not be inhibited by our first inhibition assay. This may be due to the nature of the inhibition assay. In the first assay, hHSP60 was added to the serum of the anti-hHSP60 positive patient, whereas in the second assay, hHSP60 was coated to the ELISA plate. This second assay clearly demonstrated inhibition of the anti-hHSP60 response. An explanation for this phenomenon may be that anti-hHSP60 antibodies are unable to bind to fluid phase hHSP60, but can bind to solid phase hHSP60, as demonstrated by the second inhibition assay, and the positive antibody response demonstrated in the anti-hHSP60 ELISA.

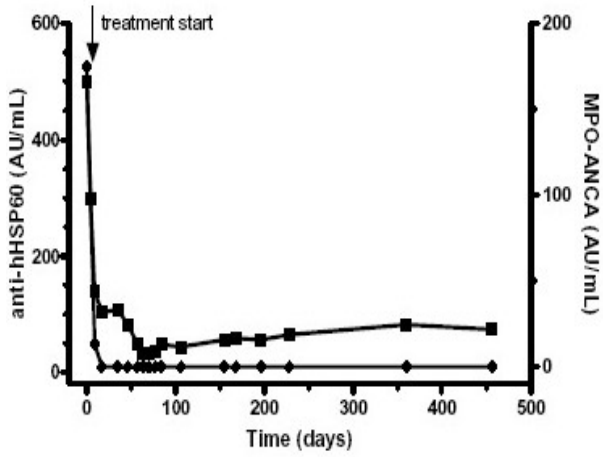

Figure 5

Follow-up of a patient positive for antibodies against human Heat Shock Protein 60 (anti-hHSP60). Anti-hHSP60 levels (■) drop as well as antibody levels against myeloperoxidase (MPO-ANCA) (_) once treatment has commenced, but increase during follow-up, while MPO-ANCA levels remain undetectable.

Conclusion

We have shown that antibodies against hHSP60 are elevated in patients with MPO-ANCA in comparison with PR3-ANCA. These findings suggest a role for infections in the pathogenesis of MPO-AAV through molecular mimicry between bacterial HSP65, human HSP60 and MPO. Additional absorption assays, however, did not support this hypothesis. Whether there is a relationship between anti-hHSP60 and cardiovascular disease in patients with MPO-ANCA remains to be studied.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

MCS participated in the design and coordination of the study, performed the statistical analysis and drafted the manuscript. RT carried out the various assays and helped to draft the manuscript. PvP participated in the coordination of the study and revised the manuscript critically. JGMCD participated in the design of the study and helped to draft the manuscript. JWCT conceived of the study, participated in its design and helped to draft the manuscript.

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CEREBROVASCULAR DISEASE ASSOCIATED WITH ANTIPHOSPHOLIPID ANTIBODIES: MORE QUESTIONS THAN ANSWERS

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Neurological syndromes occur in a significant number of patients with antiphospholipid antibodies. Theoptimal management for these patients however remains uncertain.Our study is a descriptive analysis looking retrospectively at 45 patients who presented to the principal tertiary referral centre in the Australian Capital Territory, with either cerebral arterial or venous thrombosis for which there was no obvious cause for their presentation when initially reviewed. The diagnosis was based on the clinical findings made by one of three neurologists attached to our centre. Radiological findings and the presence of either IgM or IgG anticardiolipin antibodies, IgG anti-beta-2 glycoprotein 1 antibodies or a lupus anticoagulant were then documented. In this group of patients three subgroups were identified:
1. Individuals that fulfilled the Sapporo Classification Criteria
2. Individuals with transiently positive antiphospholipid antibodies and
3. Individuals with persistently low positive antiphospholipid antibodies.
The most interesting of these three groups are those individuals with transiently positive antiphospholipid antibodies. A potential cause for presentation was identified in only one patient of this group with documented infective endocarditis and bacteraemia. Comparison with the other two groups suggested that there was little in terms of clinical presentation, radiological findings or intercurrent risk factors for thrombotic disease to distinguish between them. With disappearance of antiphospholipid antibodies, the individuals within this group have not had further thrombotic events. Our observations emphasise the problems that continue to exist in relation to the occurrence of cerebrovascular disease in the context of antiphospholipid antibodies and the optimal management of these stratified groups. Our findings also raise an as yet unanswered question as to the signficance of these transiently positive antiphospholipid antibodies. In the absence of significant intercurrent risk factors our findings would suggest that in the group we describe that they are likely to be of clinical significance.

Background

The antiphospholipid syndrome (APS) is an autoimmune disorder characterised by recurrent venous and arterial thromboses, recurrent foetal loss and spontaneous abortions, thrombocytopenia, and the presence of antiphospholipid antibodies [1,2]. While there is an association with other autoimmune diseases such as systemic lupus erythematosus, the condition may also arise independently of other autoimmune disorders [1,3,4]. The presence of antiphospholipid antibodies may also occur as associated epiphenomena related to intercurrent infectionsand in this setting are said to be less likely to be associated with the characteristic syndrome [5]. Furthermore, a number of individuals with high titre anticardiolipin antibodies do not develop APS and studies suggest that additional factors or a "second hit" are required to cause endothelial dysfunction and activation of a pro-coagulant phenotype [6,7]. Neurological syndromes occur in a significant proportion of individuals with antiphospholipid antibodies andinclude transient ischaemic attacks, stroke (either embolic or thrombotic), cerebral venous thrombosis, migraines, seizures, multi-infarct dementia and mononeuritis multiplex [2,8-10]. With strong evidence that appropriate treatment with anticoagulant therapy is effective in minimising

both arterial and venous thrombotic disease in these individuals [11,12], it is important to be able to identify individuals with APS at the time of presentation. Classification, but not clinical diagnosis is assisted by the Sapporo criteria, a preliminary classification formulated in 1999. In these criteria, venous or arterial thrombotic vascular disease is essential. The criteria currently mandate repeating antibody tests after 6 weeks [13]. This presents a problem where an acute diagnosis has implications for initiating active therapy. While a firm evidence base is accumulating for the management of venous thrombosis and recurrent pregnancy loss in APS, the same cannot be claimed for cerebrovascular disease, which remains a problematic area with a number of unanswered questions. This study involved the descriptive analysis of all patients presenting to a single centre with either cerebral arterial or venous thrombosis where a cause could not clearly be identified at the time of presentation. The presence of IgM or IgG anticardiolipin (aCL) antibodies, IgG anti-beta-2- glycoprotein1 (anti-β2GP1) antibodies and/or a lupus anticoagulant and results of radiological imaging were documented. This series of patients illustrates each of the above conundrums, and emphasises the difficulty in clear-cut decisionmaking.

Methods

Patients were selected consecutively on the basis of admission to The Canberra Hospital, the principal tertiary referral hospital for the Australian Capital Territory and surrounding south east New South Wales, with a total population of approximately 500,000, between January 1, 1995 to May 31, 2003 inclusive, with clinical or radiological evidence of cerebral infarction and the presence of IgM or IgG aCL antibodies, IgG anti-β2GP1 antibodies (when this assay became routinely available at our centre in 2000) and/or lupus anticoagulant. Initial events were recorded back to 1975 and therefore in some individuals the diagnosis was made retrospectively, in that aCL were not routinely tested for until 1986. Currently, in this institution, patients are further investigated for the presence of prothrombotic factors including AT-III, protein C and protein S deficiencies in addition to prothrombin G20210A and Factor V Leiden mutations, where there are no identifiable causes for their presentation with either cerebral venous or arterial thrombosis. Over the study period January 1, 1995 to May 31, 2003, 1729 patients were admitted to The Canberra Hospital with cerebral infarction. Following selection, clinical data were retrospectively and prospectively reviewed. For each patient the clinical findings were confirmed by examination by one of three neurologists. A number of other parameters were assessed including: intercurrent risk factors for vascular disease – hypertension, hyperlipidemia, tobacco use, obstructive sleep apnoea [14] – the presence of other procoagulant factors, the use of the combined oral contraceptive pill, a history of previous miscarriage, intrauterine growth retardation or pre-eclampsia and previous arterial or venous thrombotic events. Results of cerebral imaging, including computed tomography (CT) and magnetic resonance imaging (MRI), in addition to echocardiography and carotid duplex ultrasound, were collated. Follow-up antiphospholipid testing, ideally at least 6 weeks apart as defined in the Sapporo criteria [13] was collected where possible. Information regarding the therapy instituted at the time of diagnosis and long-term follow-up was obtained.

Laboratory tests

IgM and IgG aCL antibodies were detected by a semiquantitative enzyme-linked immunoabsorbent assay according to the manufacturer's instructions using a commercially available kit (Immuno Concepts RELISA, Sacramento, CA, USA). The test system is standardised using internationally recognised reference preparations obtained from the Antiphospholipid Standardisation Laboratory. Results were reported semi-quantitatively according to the manufacturer's instructions in standardized units as follows: negative (IgG, <8 G phospholipid

Table 1: Summary of clinical details for three groups of patients with aCL presenting with neurological events.

Demographics	Patients fulfilling Sapporo classification criteria	Group with transiently positive aCL	Group with low positive aCL
Number of patients	N = 26	N = 7	N = 12
Median age (years)	37.6 (6–63)	35.4 (16–51)	41.6 (19–59)
Number of episodes/patient			
1	19	4	6
2	7	3	6
Clinical presentations	N = 33	N = 10	N = 18
Superior sagittal sinus thrombosis	1	1	-
Higher centre function loss	3	1	1
Left hemiparesis/paraesthesia	10	5	6
Right hemiparesis/paraesthesia	6	-	2
Brainstem/cerebellar symptoms	5	-	5
Loss of consciousness/seizures	4	-	1
Fluent aphasia, right facial weakness	1	-	-
Bilateral cerebral infarction	-	1	-
Cranial nerve palsies	1	2	1
Right homonymous hemianopia	1	-	1
Transient ischaemic attacks	1	-	1
Radiological findings	N = 26	N = 7	N = 12
No abnormalities on CT or MRI scan	2	3	6
Left middle/posterior cerebral artery territory infarction	4	-	2
Right middle/posterior cerebral artery territory infarction	4	-	-
Low density area (left temporal lobe)	2	-	-
Increased signal cerebral deep white matter	3	1	2
Pontine/cerebellar infarction	2	1	1
Multiple cerebral infarcts	9	-	1
Superior sagittal sinus thrombosis	-	1	-
Bilateral narrowing of carotid syphons	-	1	-
Antiphospholipid studies:			
IgM aCL	6 moderate -high positive	-	3 low positive
IgG aCL	18 moderate -high positive	1 low positive, 1 moderate positive	6 low positive, 3 moderate positive
Lupus anticoagulant KCT	9	4	2
Lupus anticoagulant DRVVT	9	6	2
Low to moderate IgG anti-β_2GPI antibodies	7/12 (data incomplete)	1 low positive	1 low positive
Risk factors for vascular disease			
Hypercholesterolaemia	3	-	4
Hypertension	4	1	3
Tobacco use	3	2	3
Oral contraceptive pill/hormone replacement therapy	6	-	1
Pregnancy/post-partum period	2	1	-
Heterozygosity for factor V Leiden mutation		1	-
Long term warfarin	19	2	-
Warfarin (six months)	-	1	1
Low dose aspirin	6	4	10
Clopidogrel/ticlopidine	1	-	1

units (GPL units), IgM, <8 M phospholipid units (MPLunits); low positive (IgG, 8–20 GPL units; IgM 8–20 MPLunits); medium positive (IgG, 20–80 GPL units; IgM 20–80 MPL units) and high positive (IgG, >80 GPL units; IgM,>80 MPL units). IgG anti-β2GP1 antibodies were also detected by a semi-quantative enzyme-linked assay according to the manufacturer's instructions using a commercially available kit (QUANTA Lite, San Diego, CA, USA). Results were reported semi-quantitatively in standard IgG anti-β2GP1 units (SGU) as follows: positive (IgG,> 8 SGU); The system was standardised using a set of reference calibrators available from the Rheumatology Laboratory, Seton Hall University, St Joseph's Hospital and Medical Centre (New Jersey, USA) and supplied with the commercial kit. Lupus anticoagulants (LA) are a group of antibodies that interfere with phospholipid-dependent coagulation reactions. In the laboratory they are defined as prolonged clotting tests that are responsive to procoagulant phospholipids. By definition, the tests should not correct with the addition of normal plasma but are corrected by the addition of phospholipid. In our laboratory the diluted Russell's viper venom time (dRVVT) and kaolin clotting time (KCT) are used to detect LA [15]. The dRVVT is used as a screening test using a commercial kit (Gradipore, French's Forest, Australia). A mixing test is performed on all positive LA screen results, that is, the clotting time is 20% longer than the pooled platelet poor normal plasma (PNP). If the mixing test does not correct, a LA Confirm test is performed to confirm the presence of LA. The additional phospholipid in LA Confirm neutralizes lupus anticoagulants to give a normal clotting time. The KCT is performed as per the method described in Gibson et al [16], where the difference in seconds between the neat pool (10:0) and the 8:2 mixture of PNP: patient is less than 20% different from the pooled normal plasma, the sample is considered negative. Where the difference is 20% or greater then the results are graphed on a six-point curve and the shape of the curve analysed. In the presence of LA the curve should be convex in the region near the Yaxis. A platelet neutralisation procedure is then performed to confirm the presence of a lupus anticoagulant. In this procedure a frozen-thawed platelet solution is added to the kaolin clotting time mixture to provide a source of platelet phospholipid able to overcome the effects of a lupus anticoagulant. With comparison to a normal pooled plasma clotting time, normalisation of the clotting time, confirms the presence of a lupus anticoagulant. Antiphospholipid studies were repeated at least six weeks after the initial study. There have been no concerns regarding the performance of these assays in the routine quality assurance program for diagnostic laboratories in Australia run by the Royal College of Pathologists of Australasia (RCPA) and the National Association of Testing Authorities and conform with the consensus guidelines developed by the aCL Working Party comprising members of the Immunology Advisory, Quality Assurance and Scientific Education Committees of the RCPA [17].

Results

Data were collected for 52 patients and 6 were immediately excluded because follow-up serology was not available. A further patient with infective endocarditis and therefore a potential cause for the presence of aCL was also excluded from further analysis. Of the remaining 45 the median age was 38.2 years with the age ranging from 6–63 years. There were 32 females and 13 males. Three groups of patients were identified on the basis of the results of antiphospholipid antibody testing. In the first group of patients with primary antiphospholipid syndrome, 26 had completed strokes while seven of this group had had more than one stroke (two patients after anticoagulation with warfarin had been commenced). Multiple sites of the brain were involved and there was evidence for an embolic source in 8 patients. The clinical details for this group are summarised in Table 1. Twenty of the twenty-six patients were commenced on long-term high intensity warfarin therapy [11,12], either at the time of presentation or in the post-partum period. While some patients were originally diagnosed with obstetric antiphospholipid syndrome, their presentation was complicated by cerebral infarction or were noted on review during admission to have radiological evidence of past cerebral infarction.

In those patients who had contraindications to the use of warfarin – three received low dose aspirin (100 mg daily), while the fourth individual was treated with clopidogrel at the standard dose (75 mg daily). Only four patients in this group have had further thrombotic episodes since warfarinisation. The four individuals were on long-term warfarin but in all four cases the INR had fallen to less than 3.0 in the period prior to their presentation with a thrombotic event. Three of these patients had additional arterial thrombotic events. One presented with both a stroke and pulmonary embolus, while two patients had further strokes and these have been included in the study. The last patient presented with a deep venous thrombosis involving the right lower limb. The duration of sub-therapeutic INR's prior to presentation in these individuals however could not be determined due to infrequent monitoring; however there have been no further recorded recurrences subsequent to these events. The group with disappearing aCL comprised seven patients and details are summarised in Table 1. On repeat testing antiphospholipid antibodies could not be detected in any of these patients by all assays currently performed in our laboratory. Where possible these tests were performed at least six weeks after the initial tests, but in some cases were performed up to one year after initial testing. Repeated assays including LAC have remained negative and all of this group have been tested on four separate occasions albeit at differing time intervals. Only one in this group had a potential cause identified for the presentation with documented intercurrent infection. Streptococcus viridans was isolated from blood cultures and mitral valve vegetations demonstrated at echocardiography. This patient was therefore excluded from further analysis and is not included in the table. In this group, three patients received either low dose aspirin or clopidogrel where aspirin was contraindicated. The third group comprised 12 patients with persistent low positive aCL antibodies on the basis of follow up testing at least six weeks after the initial testing and clinical data are summarised in Table 1. Within this particular group there were no clear distinguishing factors on the basis of the clinical presentation. Six of the twelve individuals experienced two distinct neurological events. Within the group of twelve, six had additional risk factors for vascular disease of which five had one or two associated risk factors for vascular disease, respectively. Four of the six individuals with additional risk factors had radiological evidence of completed strokes. The majority of individuals in this group have continued on low dose aspirin.

Discussion

The three different groups of patients described emphasise a number of problems that exist in relation to the occurrence of cerebrovascular disease and antiphospholipid antibodies. Current standard practice for patients with APS is to recommend indefinite anticoagulation with warfarin. This is derived from a limited experience with arterial thrombosis, a much larger and more definitive experience with venous thrombosis and the observations by many groups that these patients are prone to recurrent cerebrovascular events which, in principle, should be preventable [11,12]. In these studies venous and arterial disease is not clearly separated and comparison between different forms of recurrence prevention is limited [18]. The Antiphospholipid Antibody Stroke Study (APASS), a prospective cohort study within the Warfarin vs. Aspirin Recurrent Stroke Study (WARSS) does not provide answers for the management of the syndrome but challenges the current practice of long duration warfarin. However, the patients in this study were not representative of those described here, or in other series of cerebrovascular disease and APS. They were generally of advanced years, the aCL cut-off was much lower than the Sapporo criteria demand and the target INR of 2.0 lower than that recommended for APS. While the subgroup of patients with both LA and aCL had a greater risk for thromboocclusive events and appeared to derive benefit from warfarin, o other group did, nor did the patients overall [19]. Patients with embolic disease were excluded from WARSS and this study and most others provide little guidance on how to deal with the patients reported here, especially the problem of how to prevent recurrent ischaemic events. There is no guidance on how to approach a patient as a primary event and

whether early diagnosis and management will make a difference to the ultimate outcome. Currently, the diagnosis is generally made after the critical cerebrovascular event is well under way, often recovering. To seriously consider how to manage these patients acutely the diagnosis would have to be appropriately acute as well. The three groups here raise some very interesting questions. Twenty-six patients satisfy the Sapporo criteria and are quite similar to other such series of patients described previously. The range of antibody tests and the nature of the cerebrovascular lesions has the same broad spectrum as has been previously described [6,15]. Based on previous experience, steps need to be taken to reduce the recurrence rate and in this series warfarin was generally used unless contraindicated. This is in agreement with the practice of others [11,12,20] although there is no clear consensus as to the optimal treatment of these patients [21] with the findings of Crowther et al [22]challenging the need for high intensity anticoagulation, demonstrating that the absolute risk of recurrent thrombosis was low where the INR was maintained at 2.0–3.0. A more recent by Finazzi et al[23] reported similar results with high-intensity warfarin (INR 3.0 – 4.5) conferring no advantage over standard treatment (INR 2.0 – 3.0) in the prevention of recurrent thrombosis in individuals with antiphospholipid syndrome and was associated with an increased risk of minor haemorrhage. Both of these studies however, excluded patients with a history of recurrent thrombosis anticogulant therapy and therefore looked at a group likely to be a lower risk of recurrent events. In Crowther et al's study, individual's allocated to the high intensity group were below the target range 43% of the time. Three of the six individuals had an INR < 3.0 at the time of thrombosis while a fourth had ceased warfarin 137 days prior to the event [22] (reviewed in [24]). It is unclear from the second study as to how frequently those allocated to the high intensity group were sub-therapeutic but the mean INR of 3.2 would suggest that at least some individuals were sub-therapeutic throughout the time of the study. These studies therefore do not necessarily refute the findings of previous groups that high intensity warfarin may confer a benefit in those at high risk of recurrent thrombosis. On the basis of the results of the Stroke Prevention in Reversible Ischemia Trial which found that high intensity anticoagulation (INR 3.0 – 4.5) was associated with an increased risk of major bleeding including cerebral haemorrhage [25,26], in addition to the small study by al- Sayegh [27] detailing haemorrhagic complications in a small group of patients with primary and secondary antiphospholipid syndrome, other groups have chosen to use low dose aspirin as prophylactic treatment in individuals with antiphospholipid syndrome who present with ischaemic stroke [28]. In our group however, 3 of the 8 patients developed further thrombotic disease while on low dose aspirin, two had recurrent strokes while the third had a spontaneous deep venous thrombosis. All three were subsequently treated with warfarin. However, it is difficult to draw conclusions based on on our study or those of al-Sayegh [27] and Derksen [28], due to their small size and lack of statistical power. Patients in the second group at the time that the first laboratory tests became available could not be individually distinguished from those in the first group in contrast to observations in a group of patients with systemic lupus erythematosus where anti-β2GP1 antibodies were noted to drop at the time of thrombosis [29]. At the initial presentation, it would be reasonable to manage them in the same way, that is, anticoagulate, however with follow-up, this was probably unnecessary as the antibodies proved short-lived and the Sapporo classification criteria were not met. An alternative approach would be to wait in all patients until the Sapporo criteria are met – that is, defer a decision on definitive anticoagulation for six weeks. Given that the risk of recurrence is probably higher early on and community based studies suggest that the highest risk is in the first year with a mortality rate of 15–20% within the first 30 days following the initial stroke [30,31], this option is not seen as attractive. Either way, when faced with the patient, especially a young patient, with a cerebrovascular event and a criteria-positive antiphospholipid antibody there is clearly a dilemma. This subgroup which we believe has not been so clearly defined before would have to be considered in any future therapeutic study. The third group also poses a problem and do not

fulfill the classification criteria for antiphospholipid syndrome, as the antibody levels are insufficient to meet the Sapporo criteria. Those without radiological abnormalities might have had migraine equivalents, but the other patients, about half with definite radiological abnormalities and low level antibodies, had very few other risk factors. While two patients within this group were given six months of warfarin, the remainder were treated with low dose aspirin. None of these patients have had a recurrence to date, with a variable follow-up of 16 months -10 years. What indeed did they have and how should they be managed? Although in serological terms these patients resemble those of the APASS study [19], they are generally much younger. In the Stroke Prevention in Young Women Study [32], where the population studies included women aged between 15 and 44 years of age presenting with a first episode of ischaemic stroke, the presence of any anticardiolipin isotype or LA was associated with an increased risk of recurrent stroke with an overall relative odds ratio (OR) of 1.87 (95% CI, 1.24–2.83, P = 0.0027). However, antiphospholipid studies were only performed on one occasion and in some cases at a time distant to the stroke. The third group reported here is hard to directly compare to these patients, but could potentially overlap substantially with the patients described by Brey et al [32], where over half the patients had low positive antiphospholipid antibodies. Although excluded from the Sapporo criteria these patients would be important in any future study, warfarin was rarely used in patients in this group in our series. This study has several limitations as it is essentially a descriptive study and is therefore open to bias given that the authors were not blinded when assessing the patients included in the study. The utility of the data is also hampered by a lack of standardisation in the approach to treatment. The assays used for assessing for the presence of aCL changed in 2000 and it is possible that some individuals may have become negative because a different assay was used. Additionally, in some individuals, the diagnosis was based on collection of retrospective data and there is no comparative group without antiphospholipid antibodies resulting in further sources of potential bias. However, a strength of this study is that it represents what is actually done in a tertiary care centre in the face of conflicting evidence. We believe that such experience is worth reporting, reflecting as it does the realities of medical practice and serving as a useful adjunct to the gold standard randomised, double blinded trial. We conclude that in our population, this combined retrospective and prospective analysis, confirms that recurrent events occur in young patients with cerebrovascular events and antiphospholipid antibodies. It does not provide information about the optimum method of preventing recurrence. Ultimately we believe there must be a much larger study of treatment and secondary prevention studies in stroke, with either emergency diagnosis of phospholipid antibody status, or a nested part of a much larger study with stratification of patients into at least the three categories described here.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

CH and PG were responsible for the initial concept, design and drafting of the manuscript. CH, PG, RT, GD and CA were involved in collation of patient data, the critical revision of the manuscript and intellectual input. All authors read and approved the final manuscript.

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Materials of the Conferences

MODELLING AND ALGORITMIZATION OF MANAGEMENT IN BIOTECHNICAL SYSTEM OF THE GAME AUTOMOBILE TRANING

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The urgency of research. The computer game biocontrol is a new rapidly developing treatment-and-improving technology at the turn of medicine, physiology, physiotherapy, electronics and programming. The basis of the biocontrol is a universal principle of the biological feedback: registered physiological parameter, the subject for correction is presented on the screen with interface, and a patient, observing his physiological function dynamically and using the skills of self-regulation, learns how to change it in a necessary for treatment direction. [M.B. Shtark, 2004].

The principle of the biological feedback gives an opportunity to the patient to become an active subject of the curing process instead of being passive object of the medical manipulations.

The urgency of the game biocontrol varients is guaranteed by the constant grows of stress, leading to numerous physiological and psychological deseases.

The computer game training apparatus contains several game plots which have an obvious or a concealed competitive character. The course of competition is regulated with dynamics of a registered physiological parameter: it may be a pulse rate, a cuteneous temperature, a galvanic skin reflex, CO_2 concentration in an exhalant air. The patient can win the competition in case if he learns how to control his physiological function in a situation of a virtual competitive stress. Colorful game plots, created with the use of the modern multimedia technologies, raise the motivation of a trained patient, contribute to more effective fixation of the autoregulation skills. [O.A. Jafarova, M.B. Sthark, 2003]. In the course of the game training a man gets an invaluable ability to resist stress and different deseases, to learn how to react on conflict situations in a new way, to reduce an excessive inner tension in that case when he needs an additional capacity for work, conation and mobilization of attention.

There are some known biocontrol games, developed in Scientific Research Institute (SRI) of molecular biology and biophysics of Russian Academy of Medical Sciences in Novosibirsk. Game hardware-software complex “Bos-Pulse” was permitted by Ministry of Health of Russian Federation for release and treatment –and – reabilitation technology of computer game biocontrol is recommended by the Academic Counsil of the Russian Ministry of Health.

It should be mentioned about the disadvantages of these games. First of all, the technical realization of the examined games is carried out in the near actual time that is connected with a sensor construction and multitask Windows environment.

Secondly, all these games are based on the control of a certain parameter, a pulse rate (magic cubes, car race, row channel skin divers), or an amplitude of B-rhythm of Electroencephalogram (planting of flowers), or CO_2 concentration in an expiration air (Martian wars). By the way, it is well-known, that the reaction of a separate organism functional system on the environmental changes always “is an integration of a large quantity of factors, none of which can be changed separately in such way to become quite efficient” [Barkroft, 1937]. It is connected with the multifrequent codes’ structure of physiological process biocontrol.

Experimental research, conducted at cell, tissues, organs level, showed that biological codes are multifrequent and their efficiency depends on a certain proportion in a complicatively modulated total signal. Also it was identified that a single wave-length action is dumped actively by an organism at the addressed level due to over – and underlying levels of homeostatic regulation. (S.L. Zaguskin, 1986).

That’s why using for biocontrol of one, even a very important parameter instead of a

multifrequent code may not be only effective, but also harmful.

Therefore, the development of biocontrol game technologies, based on the use of multifrequent codes, refers to the urgent problems of research.

The research has been done under the support of a grant РНП.2.2.3.3.3301 in accordance to the Problem Committee's plans in chronobiology and chronomedicine of Russian Academy of Medical Sciences (RAMS) and scientific work of the Faculty of Medicine in BelSU "The development of the universal devices of chronodiagnostics and biocontrol on the base of biocyclical models and algorithm with usage of biological feedback parameters."

The aim of the research: to increase management efficiency in a functional condition of a man in a situation of a virtual competitive stress due to the usage of the multiparametrial management sygnal in the form of a pulse rate, respiration rate and their correlation.

The problems of research:

To develop the algorithms of the electrophysiological data input, allowing to register, to process and to analyze mathematically the physiological signal on the line.

To formulate the models of a game plot, managed by the physiological parameters of a pulse, respiration, and their correlation.

To develop the game environment models.

To conduct the parameterization of a management model of the human physiological functions including a pulse rate dynamics, a respiration rate dynamics and their correlations.

To develop and carry out a program device of a biomanagement technology in a virtual game environment.

The methods of research: in the research will be used the methods of systematic analysis, modeling, mathematic statistics, the methods of registration and analysis of electrophysiological data in the form of a pulse and respiration sensor and an examination of rhythm.

The description of a system based on the biological feedback.

The projected system contains: a device of a pulse and respiration sensors conjunction with a personal computer and program package, providing a biomanagement technology in a virtual game environment.

Scheme (block 1) on the microcontroller plays the digitization function of analog signals (electropfysiological data input on line) from the sensors of a pulse and respiration (block 2 and block 3) with the following transmission of the digital significance on protocol RS-232.

The program part of a system is based on a automobile emulator, in which an object of control is an automobile, run with the physiological data sensors' signals according to the developed algorithm.

The structural scheme of hardware is conducted in a module execution.

The main managing element of a system is a 8 bit microcontroller PIC16F870 of Microchip, working at a frequency 20 MHz and containing 2 kb of a program memory, 128 bytes of RAM and 64 bytes of interior EEPROM memory. To organize the connection with external devices, there is a module of a universal synchronous-asynchronous transceiver USART. To receive and process the analog data in chip there is a 5-chanel ADC. The pulse sensor data (channel 1) (blocks 1,2,3), the respiration sensor data (channel 2) (block 3), and also a supply voltage data of block 10, which is done as making up of 4 accumulators VARTA (4x1,2V), comes to the analog input of a controller.

In the pulse sensor the signal is taken of a photocoupler (2), intensified in an operational amplifier (1), in which also in-phase components (disturbance) are suppressed., then the signal is gated through the filter of low frequency (4), scaled (the amplitude of a signal is brought to 5 Volts) in block 5 and is given to the analog input ADC1 of a microcontroller 6.

In the respiration sensor the signal is taken of photocoupler 3 (it consists of a light diode and photodiode, located in front of each other) and given to the analog input ADC2 of a microcontroller 6. The data of a supply voltage comes to the analog input ADC3 of a microcontroller 6.

Module 7 serves to indicate the battery's discharge and presence of a pulse sensor signal. The device is connected to the computer via port RS-232C. Microcontroller 6 exchanges data with the help of signal lines (input – RX

and output - TX) of a transceiver USART using a driver RS232C with PC9.

The device works under the guidance of program modules, a part of which is stored in the internal nonvolatile FLASH program memory of a microcontroller 6.

The structural schema of a control algorithm is shown on picture 3. In program module 2 the initialization of the main registers of the microcontroller takes place. This program part is responsible for a setup of microcontroller's hardware-software resources. Futher, according to the program the central processing device of control codes and their transmitting (codes of frequency of digitalization and activation of device) (program modules 3, 4, 5). In PM 6 the analog signals of inputs ADC 1,2,3 are transformed in to a digital form, in blocks 7,8 there is a check out on battaries's discharge (in case, if the condition is fulfilled, the discharge indicator is on and the program does in cycles.) If the condition of discharge is not fulfilled, then consistency in modules 11,12,13 a data package, consisting of a single synchrobyte, 2 bytes of digital data representation of respiration analog, and 1 byte of a control sum is transmitted on protocol RS232C to the computer.

Game environment consists of traffic lines which go through the cross-country.

Two automobiles take part in the game. The first one is run with rates corresponding to the physiological parameters of a pulse, a respiration, and their correlations. The second one is a program in accordance with given tasks.

The game begins with a joint start of two automobiles in a virtual city. Every circle passed by cars is subdivided into three parts: a virtual city, a forest and cross-country.

The city is presented with a residential area, streets, different types of houses, pavements, street lamps, trees, viaducts, fountains, side streets. The forest is represented with green plantations.

The ups and downs of a road are located in a cross-country among the hilly fields. The game is constructed in such a way, that every new circle automobiles move on a rout, quit different from the previous one. It has been done purposely to prevent the feeling of boredom and routine of a common plot with a patient.

Driving, that is changing the position of a car toward a rival car, is conducted according to a specially developed algorithm.

The control correlation is a pulse and respiration frequency.

A patient's automobile takes the leading position in a satisfying correlation of a pulse and respiration. In the opposite case the situation changes on the contrary.

To preserve a game stress situation both automobiles are well-seen to the patient, in case he becomes a loser, his rival's car is well seen and vice versa.

Different types of operators activity, which require the usage of physiological resources of activation or relaxation, have been used in the research. It depends on the usage of different strategies: directed to the success or the escape of the failure.

In the first case the player should increase heartbeat rate and the amplitude of β-rhythm of EEG. It makes the aim of increasing the speed of a playing object achievable.

The second strategy is connected with minimization of expenses, preserving the energetic resources and it is conducted with reducing of a pulse rate and increasing of an amplitude of α-rhythm.

If the player is active, his pulse grows is positive and the moving speed of the playing object is the smallest, achieving the aim becomes rather difficult.

All medical algorithms of two studied game strategies are developed by professor F.A. Pyatakovich and Assistant – professor K.F. Mackonen.

Table 2 – The algorithm of program for microcontroller

№			
1	Access point		
2	The initialization of microcontroller's registers (PIC16F870)		
3	A routine for waiting for reception of control codes		
4	Is the code has been received?	Negative	Back to routine (2-3)
		Positive	Go to routine(5)
5	Translation and execution of control codes		
6	The analog to digital conversation of signals from all analog channels		
7	K(ADC)>Klim?	Negative	Back to routine (8)
		Positive	Go to routine (9)
8	Turn on the indicator of battery discharging		Back to routine (5-6)
9	Turn off the indicator of battery discharging		
10	CRC calculation		
11	A routine for synchro-byte of frame beginning uploading to USART		
12	A routine for uploading of counts (channels 1 and 2 of ADC) to USART		
13	A routine for CRC uploading		Back to (5-6)

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MECHANISMS OF HISTOGENESIS AND CYTOMORPHOGENESIS OF EPITHELIOID CELLS IN CHRONIC GRANULOMATOUS PROCESSES. THE FACTS AND HYPOTHESES

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It is known that during an embryogenesis the number of cell-like types will be derivated strictly particular for each species of organism, each of which has only to it intrinsic morphophysiological characteristic. One cells function only at particular stages embryonal development and then fade in outcome apoptotic death, others, on the contrary, are characteristic only for an adult organism. However, in researching granulomas forming at some granulomatousis diseases, already for a long time the cells were circumscribed which are not occur in a healthy organism. To number of such cells referred «basophilic hystiocytes» in rheumatic disease, Mikulich cells in scleroma, epithelioid cells (EC), formating epithelioid cell granulomas in a number of infectious, allergic and autoimmune diseases, and also other forms of atypical cells.

It was shown that EC forming in the nidus of the inflammation in granulomatousis diseases of different etiology. Suppose that EC do not enter number of differentiated cell-like types neither embryonic not adult organism; they occur only at particular pathological statuses and forming EC-granulomas. This granulomas determine clinicomorphologic essence of many granulomatousis diseases in man. Moreover, the EC-granulomas form in different groups animals relating to different branches of "phylogenetic tree". Thus, epithelioid cell formation in the nidus of inflammation can be related to one of most ancient mechanisms of cell-like response on imbalance of the «antigenic-structural" homeostasis in organism.

The concept of EC origin from cells of macrophage family till now is considered conventional, which some theoretical fundamentals were hypotheca in workers of Ashoff L. (1924) and Maksimov A.A. (1926). Affirms that EC transform from macrophages (Mph) located in the nidus where the pathological process flows past and under some conditions - directly from monocytes of a blood. This concept undations on a hypothesis that in a basis of the differentiation resulting in to derivation EC from Mph in reply to particular

pathogenic stimulus lie the changes of genic activity, and that in a basis of this transformation resulting in to formation EC lie epigenetic of changes, and the phenomenon can be considered as "intra-tissue transdetermination" (Shvemberger I.N., 1976). Important thus to mark that till now is not obtained enouph convince facts touching not only the mechanisms of transformation of Mph into EC, but also process of series transformation of Mph into EC. It is explained to that indicated the concept and hypothesis based, mainly, on the results of classic morphological researches, in which, as well as in many modern morphological works, registered only the fact of appearance of EC in populations of cells of macrophage type without the analysis of the transition forms from Mph to EC. It is necessary thus to underline that in none of works dedicated search of EC metastructure, is not obtained of enough convincing and indisputable evidences of existence of the legible transition forms between Mph and EC. Moreover, there are no convincing facts which would testify that differentiated Mph can undergo differentiation that is switch on in the process being a basis of possible conversion cell-like phenotype.

At usage of cell-like technologies in learning EC cytomorphogenesis we obtained the in essence new facts which have forced us to refuse the concept of origin of EC from Mph. The application of different cell-like technologies (cultivation in vitro, transplantation of cells in vivo, explantation of cells of granulomas in cultures) allows to place that among peritoneal cells, mononuclear blood cells and bone marrow exist low-differentiated cells - EC-precursors (pre-EC), distinguishing from cells of macrophage series on number of cytomorphologic identifiers registered in vitro (Arkhipov S.A., 1996). Obtained data allow us to confirm the hypothesis expressed earlier (Arkhipov S.A., 1995) that exist unipotent precursors EC (pre-pre-EC) which differentiate only into EC at defined conditions combined in the nidus of chronic inflammation. All stages of differentiation of pre-EC into mature cells of epithelioid type possessing about proliferative activity are defined. On the basis of the obtained data lay down the new conception of origin and differentiation of EC (Arkhipov S.A., 1997). The essence of this concept is that EC is concidered as a terminal link of differentiation of a separate hemopoietic line of cells histogenetic independent from granulocyte-macrophage direction of a hemogenesis from which at particular pathological processes differentiate all types of EC. Is was shown that of EC-germ forming in norm quantitatively restricted population of low-differentiated monocytoid blood cells being committed cells-precursors of EC. In cronic inflammation the pool of pre-EC in organism increases. By cytomorphologic characteristics pre-EC were referred to the class of reticular cells.

Now we obtain the new experiment data indicating the existence a genetic determinancy of a datum basal level epithelioid cell reactivity concerning different inductors of an inflammation. Set a question on correlation between function and phenotypic variation of EC. Data obtained directing that the morphogenesis epithelioid cell granulomas might determine by the several factors: initial genetically determinate level of a pool pre-pre-EC, inflow pre-EC, committed in EC trend of differentiation in the nidus of inflammation, and also intensity of processes of their proliferation and differentiation.

The data obtained by us allow in a new fashion to formulate a hypothesis about a probable origin and early stages of a histogenesis EC, namely that EC might the descendants of mesenchymal stem cells of a bone marrow parentage, out of which differentiate some stromal cells of organism. Apparently the verification of this hypothesis is inconceivable without usage of new modern cell-like technologies. The clearing up of early stages of EC histogenesis will allow to answer the question not only about biological essence of EC formating in different chronic granulomatous processes, but also more precisely to spot their function assignment in an organism at pathology.

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THE CONTENT OF NUCLEIC ACIDS IN TISSUES AND PIG PRODUCTIVITY

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New methods to evaluate animals require the study in interior indexes in relation to meat traits.

The improvement of breed and productive traits of pigs is largely determined by biochemical tests which reflect metabolism intensity in animal organisms.

Nucleic acids accomplish the storage and transfer of genetic information and are involved in realization of the information through the synthesis of all proteins.

Methionine plays an essential part in protein metabolism; it is the only amino acid that initiates the protein synthesis.

Proteins provide multiversity of functions in organisms and phenotypic characters. They are molecular instruments which accomplish the realization of hereditary information. Proteins make up about a half of dry weight of living organism. Muscular tissue contains around 72 – 80% water, dry matter largely composed of proteins making up 20 – 28%.

The experiment was carried out on the experimental training farm “Tulinskoye” of Novosibirsk State Agrarian University. The object of research was Precocious Meat pigs (SM-1) which are well adapted to local natural and climatic conditions.

The research was done in the 6 month animals in control fattening. The pigs were kept according to the technology provided for complexes and farms. The data was processed statistically through computer programs MS Excel 2000, Statsoft Statistica 6.

The progeny from 6 boars of Precocious Meat breed were under control in the experiment. Individual variation of methionine content in blood serum, DNA, RNA and liver protein in progenies from different boars were explored. Liver was chosen for the exploration because it was regarded as the organ with the expressed function of protein synthesis.

It was established that the pigs different in economically valuable characters differentiated by the explored biochemical indexes. The animals with improved meat productivity were revealed to have higher DNA and RNA content. Protein level in liver was determined to vary with meat traits and to be higher in the individuals with higher ham weight (11.06%, $p<0.01$). Gilts of longer carcass exceeded those of the same age for the concentration of methionine in blood serum (8.73%, $p<0.05$).

The higher content of DNA, RNA, methionine and protein was identified in the blood serum and liver of the progenies from the Svetly 1704 and the Soviet 1618 and this testifies to the higher intensity of protein biosynthesis in the tissues of the pigs with improved productive traits.

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THE FEATURES OF THE 2ND TYPE DIABETES MELLITUS IN ABORIGINAL POPULATION OF THE NORTH

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In the Republic of Sakha (Yakutia) the 2nd type of diabetes mellitus (DM 2) is the most wide-spread pathology of endocrine system. (P.M.Ignatiev, M.A.Fedorova, 2004). For the last decades DM 2 disease incidence has increased more than 2 times. Considerable and fast growth of DM 2 disease has been observed especially among aboriginal population of the North. Undoubtedly the spread of this "metabolic" epidemy is closely connected with urbanization of the North, deformation of traditional food of natives and other factors. Nowadays observation of indigenous inhabitants with DM 2 gives us an opportunity to analyze the features of their disease process, compensation, late complications etc.

Materials and methods. We examined 68 Yakuts (49 women and 19 men) with DM 2 who

were on hospitalization in endocrinological department of Republican hospital № 2 of Emergency Medical Care Centre during the period 2002 - 2005 (group 1). Average age of patients was 58,16±1,12 years. Diabetes duration was 8,4±1,36 years. For comparison we examined 32 Russian patients (21 woman and 11 men) with DM 2 of the same age (group 2). In this group diabetes duration was 11,8±1,52 years. They were put diagnosis DM 2 on the basis of classification and diagnostic criteria of the WORLD ORGANIZATION OF PUBLIC HEALTH (1999). Anthropometrical parameters of research included weight, growth, dimensions of waist and hips as well as calculation of the index of body weight (IBW) and ratio of waist and hips (W/H). All the patients filled in the form for revealing social data, anamnesis of chronic diseases and uses of medicines. This form also contained questions about food (dietetical interview), physical activity, ischemic disease of the heart heredity and harmful habits (smoking and alcohol). All the patients gave their consents to participate in research, including biochemical analyses conduction.

Laboratory methods of research included:

Definition of blood sugar within a day (glycemia profile) by glucose oxidant method with automatic biochemical analyzer "Eos-bravo" of Hospitax-diagnostics (Switzerland - Italy) in biochemical laboratory of Republican Hospital № 2 (EMCC). Definition of glycosylated hemoglobin - HвA1c by liquid chromatography under pressure (normal level of 4,5-6,2 %) in a laboratory of polyclinic №1 in Yakutsk. Glycemia and HвA1c were evaluated according to WORLD ORGANIZATION OF PUBLIC HEALTH specifications, 1999.

Definition of lipid spectrum in blood serum by diagnosticum in vitro method(TC, HDL, TRG, LDL, non-HDL, TC/HDL) with the help of standard cartridges on the device CHOLESTECH LDX (USA) after the 14 hours night starvation period and 3 days with no alcohol. Classification ATP III was put on a basis of lipoproteins levels interpretation.

Clinical examination included arterial tension measurement by A.S.Korotkov's method, electrocardiogram, ultrasonic research of abdominal cavity, echocardiogram.

All patients were examined by internist, oculist, neuropathologist, podiatrician (the expert on diabetic foot) and surgeon.

Statistical data processing was carried out by means of BIOSTAT 3.03 and Microsoft Excel Programs (version 7.0). In cases of distribution close to normal the data are presented as M ± SD (M is an average arithmetic, SD - standard deviation). Quality datas are presented as absolute quantity of examinations and percentage (%) of the patient's quantity according to the sample or the appropriate group. In case of distribution close to normal we applied Student's t-criterion for two samples comparison. Distinctions were statistically significant at $p < 0,05$. The correlation analysis was carried out with the use of Spirman's rank correlation.

Results and their discussion. The analysis of the basic anthropometrical data in 2 groups has revealed lower parameters of growth and weight in group 1 in comparison with group 2. 23 Yakuts (33,8 %) with DM 2 suffered from expressed obesity (IBW>30kg/m²). The percentage of Russian patients with obesity was a bit higher (53,1 %). According to dietetical interview 35,2 % of people of the group 1 mainly feed on dishes of national kitchen compared to 15,6% of group 2. Most patients (group 1) with obesity (60,9 %) preferred the European meal. More than 30 % of respondents of both groups estimated their physical activity as hypodynamia (35,3 % и31,25 %). According to HвA1 level compensation of DM 2 was observed with 19 people (27,9 %) in group 1 and 10 (31,2 %) in group 2. Decompensation was marked with 24 (35,3 %) patients in group 1 and 11 (34,4 %) in group 2. The comparison of DM duration revealed that more than a half patients of group 1 (76,6 %) had suffered from the disease for less than 10 years, 54,4 % of them – about 5 years. In group 2 the percentage of people suffering from DM for more than 10 years was 43,8%. Nevertheless, the frequency of late complications in both groups was mainly identical. We found out that patients had diabetic angioretinopathy (79,4 % and 71.8%), neuropathy (72 % and 71,8), nephropathy (57% and 59,3 %), fat hepatosis (52,9% and 53,1%), diabetic foot (13,2% and 12,5%) and dislipidemia (60,2% and 68,7 %). 36,7 % of the

1st group patients and 62,5 % of the 2nd had ischemic disease of the heart . In the 1st group there were 5 patients with infarct of myocardium, 3 of them had "muted" form, and 4 had arrhythmia. 42 % of patients of group 1 and 62 % of patients of group 2 were put a diagnosis aorta atherosclerosis with transition to the base of velum of aorta and mitral valves. 60% and 65% accordingly suffered from arterial hypertension (Blood pressure > 140/90 mm.Hg). Ultrasonic research of abdominal cavity revealed signs of pancreatitis with 84 % of the 1st group patients and 61 % of people of group 2. Approximately identical quantity of patients had signs of cholecystitis, gallstone, pyelonephritis, urolithic illness. Biochemical parameters revealed authentic distinctions of lypoproteid level ($p < 0,05$) of high density (HDL). The 1st group patients had higher level of HDL (1,42+0,12 ммоль/l) in comparison with parameters in group 2 (0,76+0,13 ммоль/л).

CONCLUSIONS. The examination of Yakuts showed that diabetic microangiopathia of various degrees is diagnosed with the duration of disease up to 10 years. Thus, searches of the various genetic factors providing higher or lower susceptibility of microvascular bed of target organs to the influence of metabolic factors are proved. As for macrovascular complications, the ischemic deasease of the heart incidents among native people of the North are revealed more rarely than among Russians, possibly due to protective action of high level of high density lipoproteins**.** Clinical features of ischemic disease of the heart with Yakuts suffering from DM indicate that they have autonomical neuropathy.

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THE INFLUENCE OF A NEW ANTIOXIDATIC PREPARATION ON THE REPRODUCTIVE FUNCTION OF MALE-RATS

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In the group of N_9 – substituted of Imidazobenzimidazoles it has been revealed a new antioxidatic substance, surpassing of an antioxidant preparation of mixidol (V.A.Kosolapov, 2003) in efficiency. Toxicological researches proved that this substance is less toxic. LD_{50} is 1680 mg/kg, the therapeutic index is 336 c.u., in intragasric administration, but a safe diapasone of therapeutic activity is 12 c.u. in which the dose of 5 mg/kg corresponds to the lower level of safe therapeutic action, and a dose of 60 mg/kg - to the top level. Thus, the gonadotrophic properties of this substance were subjected to investigation in further reseaches.

The purpose of the present reseach was to study the influence of a new antioxidant substance on the generative function of male-rats.

The experiments are carried out on 90 male-rats (60 males and 30 females) with the mass of 180 gramm, keeping the rules of the International convention on the protection of the vertebrates (Strasbourg, 1986).

During the researches the males have been subdivided into 3 equal groups. The investigated substance was introduced per os in a dozes of 5 and 60 mg/kg, (1 and 2 group) for 2 months, the 3-rd group was intact. A sexual behavior, the spermiogramme have been studied and a gonad morphometry was performed. The duration of latent period and sexual activity, the number of approaches of male to female and number of coupling with intact female-rats were studied. To investigate the male's spermiogramm male-rats were subjected to ether narcosis. The testicles and epididymis were exracted. The spermatic substance from epididymis was taken to calculate number of normal and pathological forms of spermatozoons and period of their motility. Testicles were subjected to histological

processing for morfometry's research. Statistical data processing was carried out with Microsoft Exel programme.

As a result of researches it is revealed, that the latent period reduced (20-30 %) and duration of sexual activity increased in male-rats of 1 and 2 groups. At the same time, the amount of male's approaches to females increased 2,5-fold in time the 1-st group of male-rats. Then, the same changes in males of the 2 group was found in a lesser degree (10-15 %).

The reliable growth of total number of spermatozoons (17 and 34 %) and the prolongation of the period of spermatozoons's motility 15 % was revealed in spermiogramm of experimental groups of males at the same time.

The amount of pathological forms corresponded to the control rates. The tendency of decreasing of gonads mass coefficient (10-12 %) and growth of epididimys mass coefficient (8-10 %) was revealed during gonads's morphometry in males, receiving the substance in dozes of 5 and 60 mg/kg.

It is established, that the index of a spermatogenesis in these animals did not change, and the canaliculuses's number in testicles with the desquamated epithelium increased

The results of researches showed that new antioxidant substance of some N_9 -substituted of Imidazobenzimidazoles activates the sexual motivations of males, stimulates spermatozoons's emission from testicles to epididymis and influences the morphostructure of gonads's canales, depending on the dose.

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KARYOTYPE CHANGE OF CEREBRUM CELLS IN LEUKAEMIA DISEASE

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Leukaemia (leucosis) - is a system progressing accrementition of the primitive tumor burden in blood-making organs with hematogenic dissemination in other organs and tissue. The etiology of leukemogenesis is factors, which can cause the mutation of blood making cells: Viruses, Ionizing radiation, Chemical agents, Immunodeficiencies, Genetic factor, Panmyelophthisis.

The foundations for the diacrisis of the oncohematological diseases were layed down by the works of the A.A. Maksimov's followers, the hematologists I. L. Chertkov and A. Ya. Fridenshtein. The 5th level of survivability of the patients with hemoblastosis is still low. There are initial changes of the karyotype among the variety of the chromosomal anomalies. Such changes are typical for the certain variants of leukosis and concern the disease process. The changes in structure, with oncogene, growth factor gene, cell receptors and other bioactive genes involved, attribute to the initial and specific changes of chromosomes. The transgenesis, gene activation and loss, which control the oncogene functioning in the normal genome, and also the new DNA sequences formed by the translocation, play a great role in the processes of the neoplastic mutation. While working we have found the following cytogenetic changes:

del(6)(q21); 45,XY(-3); der(17); 45,XY(-7); t(15;17)(q21;q22); t(9;22)(q34;q11); inv(16); t(11;19)(q23;p13); inv(8)(p11;q13);

the polyploid variants of cerebrum cells karyotype. There are also nonspecific or post primary aberrations, which can come cause of the neoplastic proliferation and represent the processes of cloned evolution of leukemia cells. The post primary changes are not unique. The same changes are described in the different neoformations. But such changes present in the karyotype of the patients and have influence on the course of the disease. In recent years the great attention was paid to the role of some

genetic anomalies in the course of different forms of leukemia. The traditional cytogenetic methods and extremely sensitive anti-transcriptase polymerase reaction (RT-PCR) are widely used for finding out these anomalies. The first step was taken by us. We have defined such changes as:

inv(16)(p13;q22)/CBF/MYH11;t(4;11)(q21 ;p15)/NUP98/RAP1GDS1;
t(11;19)(q23;p13)/MLL/EEN.

These anomalies are not notable for the exact linearity and perfectly register FAB-variants, except for the acute non-lymphoblastic leukemia, variant M3, when in 95 per cent of the cases are defined as t(15;17)(q22; q21)/PML/ RAR. The diagnostics of the chronic myeloleukemia and other chronic myelo-proliferative diseases and leukemoid reactions widely use the concept Philadelphia (Ph') chromosome, formed by the translocation t(9; 22)(q34; q11) or hybrid gene BCR/ABL. The using of the cytogenetic and molecular and genetic analysis while collecting the data of immunophenotyping is the 3^{d} level of the hemoblastosis diagnostic. We consider it to be used in the nearest future in order to solve difficult diagnostic problems and give a possibility to point out some nosologic forms and variants of the onco-hematological diseases, which are notable for the mechanisms of forming, clinical and hematological and prognostic features, and optimal methods of therapy.

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STRUCTURE OF THE MODELS AND ALGORITHM OF THE CYCLICLE BIOCONTROL IN COMPUTER SYSTEM OF THE MILLIMETER THERAPY

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Urgency of the study. In 1978 CHzhou Lini in China has voiced the suggestion about that that at irradiation of the person weak, but broadband spectrum of the electromagnetic waves organism "itself by itself" perceives lacking him electromagnetic fluctuations. This was exactly he, who has for the first time executed hardware realization given to ideas, in accordance with which medical device generates the electromagnetic fluctuations with small spectral density, but in broad band of the frequencies, including infrared and extreme high frequencies (EHF) ranges of the waves.

In 1993 F.A. Pyatakovich, S.L. Zaguskin, T.I. Yakunchenko have for the first time developed system biotechnical, founded on biocontrol amplitude-frequency inflexion millimeter of the range of the lengths of the waves. The Clinical acknowledgement considered above of the ideas was received at treatment to complicated peptic ulcer with the help of biocontrol way millimeter therapy [F.A. Pyatakovich, T.I. Yakunchenko, 1997, 2000,2003].

It Is considered and matrix way to realization millimeter influences on base three avalanche stairwell diode (ASD) [L.A. Krupenikina, O.V. Maslova, 2001; T.I. Yakunchenko, F.A. Pyatakovich, L.A. Krupenikina, 2002].

The Way was founded on chronobiological principle to inflexions with use parameter to biofeedback.

In designed author to system effectively functioned whole only three programs of the influence, intended for correcting immunological and rheological of the breaches beside sick sugar diabetes.

These restrictions were connected with hardware system of the realization millimeter radiations and use in her ROM. Consequently,

actual is a development computer software operated systems millimeter therapy, founded on matrix way of their realization.

The Purposes and problems of the study: development system acceptance biodirection, onruled on personalization and reinforcement to efficiency of the influence, in accordance with development and use matrix specialized device in computer biocontrol system for millimeter therapy.

For achievement delivered purposes necessary to solve the following problems:

conduct the analysis of the perspective directions, in accordance with decision of the reinforcement to efficiency medical technology with use matrix millimeter influences, marketed in a milieau of computer biocontrol;

consider the probabilistic models of the pathological conditions, referring to gynecologicals diseases and intended for categorization metroendometritis , endometriosis and diffuse of the form fibromioma;

develop the general structured models reception millimeter of the waves on base hexagonal schemes matrix radiation;

form to models and algorithms of programme control intensity influences, founded on electoral use poles matrix radiation by electromagnetic flap EHF-range by means of synchronizing them with parameter to biological feedback;

consider the results of the studies on influence of the electromagnetic radiation extremely radio frequency millimeter range of the lengths of the waves on base hexagonal schemes matrix radiation on current of the pathological process under some gynecologicals disease.

In work were used methods of the system analysis, modeling, mathematical statistics, methods to registrations and analysis electrophysiological to information in the manner of heart rate variability (HRV), information analysis HRV and EEG.

For entering electrophysiological to information in mode on line us was used external device on the base monocrystal microcontroller of the company Atmel. The Device includes the sensor of the pulse, which correct works with all operating system family Windows, using standard name port COM1 or COM2. His possible disconnect and connect in hot mode that is to say, not producing switching off the superblock of the computer.

On base conditionally-probabilistic models, aproximated by differential law of the distribution, were received information features of the microstructure rhythm heart with calculation main parameter to entropy. These factors served the central to categorization degree to activities of the autonomous nervious system.

In study are presented methdological acceptance of modeling of the structure receptions millimeter of the waves, founded on biological principle. The Genetic system of the person includes the symbiosis to spirals desoxyrhybonucleinic acids (DRA) with protein - histon, which are united in structure hexagonal nature. DRA-matrix (the double spiral 2x2) does 2,5 turns around each histon, going consecutively to the following, shifted on 1/2 periods under corner 60^0, forming as a result architecture look like corn cob. The Anisochronous engine or generator are a copy given to designs.

Any external electromagnetic background causes in double spiral DRA electromoving power (EMP) i.e. DRA begins to work as perceiving antenna, but inwardly designs appears the revolvinging electromagnetic field. Histons also present itself complex protein, on essences, presenting information "diskette-resonator".

The Logical continuation considered models receptions millimeter of the waves was a development hexagonal structures matrix receptions, consisting of poles EHF-generator and providing shaping revolving electromagnetic field.

We consider six models (molded) millimeter influences.

Table 1 Codified model to switchings EHF-generator, generating revolving electromagnetic field

ormula	**Order to switchings generator**	Frequency **GHz**	**Order to realization of the formula in beats of the pulse**			
			N umber of cycles	**Rep etition cycles**	**ause**	**Tim e**
	2	**3**	**4**	**5**		**7**
-4	**a-c-b-a_1-c_1-b_1 a-c-b-a_1-c_1-b_1**	**42-53-60-42-53-60 42-53-60-42-53-60**	**21 12**	**9*3 3=298**	**0**	Transition to formula **F-5**
-5	**a-c_1-b-a_1-c-b_1 a-c_1-b-a_1-c-b_1**	**42-53-60-42-53-60 42-53-60-42-53-60**	**21 12**	**9*3 3=298**	**0**	Transition to formula **F-6**
-6	**aa_1-cc_1-bb_1 aa_1 cc_1-bb_1**	**42-42 53-53 60-60 42-42 53-53 60-60**	**21 12**	**9*3 3=298**	**0**	**Tra nsition to formula F-4**

In persisting work is considered computer biotechnical system, which contains the chronomodule of the breathing and pulse, hexagonal matrix from six avalanche- fly diode with different therapeutic length of the waves: 7,1 mms (42,2 GHz); 5,6 mms (53,5 GHz); 4,9 mms (60,5 GHz).

The First formula (F-1) includes the medical action to combinations of the frequencies 42,2; 53,5; 60,5 GHz with maximum use the frequency 42,2 GHz (7,1 mms). The Second formula (F-2) includes the medical action to combinations of the frequencies 53,5; 60,5; 42,2 GHz with maximum use the frequency 53,5 (5,6 mms). The Third formula (F-3) includes the medical action to combinations of the frequencies 60,5 53,5 42,2 GHz with maximum use the frequency 60,5 GHz (4,9 mms). In base of the realization molded the influences F-4, F-5, F-6 (tabl.1) mortgaged possibilities to switchings radiations in hexahonal to matrix, generating revolving electromagnetic field.

In formula F-4 use the sequence to switchings EHF-generator, located under углом 120 degrees. Cut-in EHF-generator (42-53-60 GHz) occurs consecutively.

Herewith periodic change position is realized with a-c-b on a1-c1-b1 (fig.3 and fig.4).

In formula F-5 use consequent switching EHF –generator (42-53-60 GHz), located on move of the hour hand.

Herewith periodic change position is realized with a-c1-b on a1-c-b1.

In formula F-6 use the sequence to switchings EHF -generator, located under углом 180 degrees. Cut-in fresh EHF -generator (42-42 53-53 and 60-60 GHz) occurs consecutively.

Herewith periodic change position is realized with aa1 on cc1 and on bb1 (fig.6).

Each program is repeated in cycle since period of the slow first-order wave by duration in 33 beats of the pulse. This period corresponds to the rhythm an intersystemic relations. Moreover 21 beats of the pulse accounts for period with maximum factor of the filling the signal and 12 beats of the pulse - for a period of with maximum porousity of the signal.

The repetition of the cycle 9 once provides time to realization equal 298 beats of the pulse (9 h 33 =298) that approximately corresponds to five minutes of physical time. On length following 60 beats of the pulse is realized pause, when influence is absent.

Under the individual normal fluctuation interpulse interval from 0,66-1,00 with realtime of the procedure, including worker cycle and pause, will form 3,94-5,97 minute [(298+60)*0,66/60]=(358*0,66)/60=3,94 and (358*1,0)/60=5,97 minute. Clean time of the influence (without pause) will form (298 * 0,66)/60=3,28 minute and (298 *1,0)/60=4,97 minute.

The Amount of the repetitions is defined by duration of the procedure: 298 beats of the pulse

(beside 5 minutes), 596 beats of the pulse (beside 10 minutes), 894 beats of the pulse (beside 15 minutes), 1192 beats of the pulse (beside 20 minutes), 1490 beats of the pulse (beside 25 minutes), 1788 beats of the pulse (beside 30 minutes) e.c.t.

The Realization of the influence is realized in software-operated mode, providing change the frequency and duration pulse influences with beat of the pulse and breathing of the patient in tact. The Biological feedback includes respiratory and heart-vascular system, sensor of the breathing and pulse, summer, width-pulse modulator, software-rememberring device, electronic commutator, wave-conductor with radiation antenna.

Use acceptance bioadaptive of control was provided at realization matrix millimeter therapy directed on modification of the condition patients in the manner of relaxations. The Main correlations of the frequency of the pulse and respiratory cycle reductions, as well as period of the functioning and pauses for all programs of the influence were an realized with use of forced control breathing.

The Program to realization of the forced breathing includes six molded the influences with consequent realization millimeter impulse of the radiation, duration and pauses which depends on correlations of the number heart beats and cycles of the breathing: 3:1; 4:1; 5:1; 6:1; 8:1; 8:1.

Each formula of the influence of the program is realized in strict correspondence to with algorithm of the switchings ASD-radiations, recorded in ROM device.

The Formula of the influence cyclical is repeated. Herewith, one cycle of the influence is divided on two consecutively executed part. The Influence at will user is assigned number amount reiterative cycles from 1 before 7, including each period of the functioning in 300 beats of the pulse and period of the pause in 60 beats of the pulse.

In program herewith use the mode "synchronizing the forced deceleration of the breathing".

This mode realizes synchronizing impulses radiations with frequency of the heart beats and breathings reductions of the patient, but on special algorithm, when realize the fluent deceleration of the breathing before correlation 8:1. In this case on special to straightedge indicator must be flashed signals of the breath, pauses and exhalation. The Light signals of the breath-pauses-exhalation are flashed at moments of the appearance signal pulse. Analysis is provided in program on correspondence to of the velocities of the breathing and pulse on special chronodiagnostical algorithm.

Biocontrol change the influence EMR is concluded in cyclical switching ASD - a generator of the different frequency synchronous in tact with beats of the pulse inwardly respiratory cycle, defining different duration useful carrying signal: at moment of the systole and on breath duration pulse most, but at moment diastole and exhalation- least.

In work are considered deterministic models of the pathological conditions endometrium and myometrium in the manner of codified matrixes syndrome on base of the parabolic dependency symptoms ($Y= X^3$). The Designed system to formalizations signs for differential diagnostics metroendometritis, diffuse of the form endometriosis and fibromioma. The formalized history disease contained 38 signs.

The Quantitative signs, being half way between itself in parabolic dependency, have served the base for development of the differential diagnostic system to categorizations considered pathological conditions.

Use given diagnostic system is calculated for selection sick on undertaking optimum therapy, including computer software operated millimeter therapy. Clinical verification has shown that algorithm possesses high sensitivity (91,5%) and specificity (81,8%) that reflects his(its) differential - a diagnostic possibilities.

The Estimation to efficiency of the treatment with the help of software operated matrix millimeter therapy was conducted beside 60 womans with metroendometritis, complicated adnecsitis on background base therapy. Herewith, two modes were used: 1) false millimeter therapy, when device was enclosed and installed matrix radiation, but without electromagnetic radiation (the mode placebo); 2) mode software operated influences

with the help of included hexahonal of the matrix.

In group sick got real millimeter therapy was noted full disappearance of the syndrome to pains beside 70 % sick after course treatment. The difference this statistical reliable ($p<0,001$).

Realistically more often met having weak and moderate pain in group sick cured with the help of real software operated matrix millimeter therapy.

After rate software operated millimeter of the action is noted reduction of the level anxious situation of patient: realistically increased the share sick in low-level class (79%) anxious situation and realistically fell the share sick, having sparingly increased (16%) and high level (5%) anxious situation.

The dynamics reorganize internal structure of the rhythm heart is indicative of reduction level adrenergic mechanism and increase the contribution cholinergic mechanism of regulation (the table 2).

Table 2 Indexes to information model of the microstructure rhythm heart

information parameters of model	**Regime of millimeter therapy**			**Module of difference**		
	Date initial	**Regime placebo**	**Regime real**			
	P_1 %	**P_2 %**	**P_3 %**	**$P_1 – P_3$**	**$P_1 – P_2$**	**$P_2 - P_3$**
Accelerate correction	**4**	**2**	**10**	**2**	**8**	**6**
Zero correction	**96**	**93**	**65**	**3**	**28**	**31**
Delay correction	**0**	**5**	**25**	**5**	**20**	**25**
$S\|P_{i1}-P_{i2}\|$				**10**	**56**	**62**
$D(x_i)$				**5 %**	**28,0%**	**31%**
P				**> 0,05**	**< 0,05**	**< 0,05**

What follows from presented in table 2 data, pattern of microstructure rhythm heart at period small variability nearby interval was charaterized by before treatment. Zero correction formed 96% all interval. Consequently, was noted sharply expressed a prevalence of the adrenergic mechanism regulation. When use placebo mode has not occurred reliable change the internal structure of the rhythm heart.

Only after course software operated matrix millimeter therapy noted reliable shifts microstructure rhythm heart. In particular, decreased the share zero correction before 65%, increased the share slowing correction before 25% and increased the share accelerating correction before 10%.

The Nature of the change parameter EEG, herewith, reflects the normalization an neurodynamic processes to brain activity, directed on reinforcement of the reactions of the braking.

Concluding as a whole, follows to emphasize the system nature, rendered on sick with pathology feminine sexual spheres, influences software operated matrix millimeter therapy, used in mode biocontrol.

Conclusion:

1. The Formed system of the slicing parameter in the aggregate presenting codified to models, realizing effects revolving electromagnetic field, differring by hexagonal location of the radiations in leading matrix.

2. The designed chronodiagnostic algorithms for computer software-operated millimeter therapy, differring by biocyclical principle of control influence extremely high frequency radiation in hexagonal to matrix.

3. They Are Created structure of the models and algorithm of computer control intensity

influences, directed on optimization of the medical influence, differring differentiated by use hexagonal radiating matrixes, timed parameter to biological feedback;

4. The marketed algorithms of the analysis and processing to clinical information in the manner of automated module, directed on recognition metroendometritis, endometriosis and diffuse of the form fibromioma and differring way of the coding to information in the form of the parabolic dependency signs.

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DESIGN OF MECHATRONICAL UNIT WITH CAM ACTUATOR FOR ARTIFICIAL HEART VENTRICLE

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Last years in the world the tendency of increase in quantity of operations on implantation of the mechanical devices supporting heart activity as change of donor organ is connected with many insoluble biological and social problems is observed and cannot provide all needs. Today completely to satisfy need for donor hearts it is not possible, therefore the problem in creation of autonomous implanted systems of auxiliary blood circulation and artificial heart is extremely actual.

In the decision of this problem it is possible to allocate two basic directions: constant replacement of natural body with an artificial limb completely replacing pump function of heart and capable long years to support blood circulation that is total artificial heart; temporary replacement of function for the period of treatment of the heart before recovery of its functional ability. Methods of the temporary heart assistance and replacements of its delivery function by the mechanical devices relate to the last direction incorporated by concept « auxiliary blood circulation ».

By development of the mechatronical module of left ventricle assist device (LVAD) with executive mechanism of cam actuator type it is necessary to adhere to requirements of reliability of maintenance of a continuous flow in the system of blood circulation at given antipressure and a low trauma of blood, maintenance of stability of work at pulsing change of pressure and the charge on its input. It should guarantee full tightness of the working cavity of the pump in relation to the environment, have the minimal sizes and weight for implanted variants of application, a low level of pulsations and noise. Researches have shown, that this mechatronical module at the given characteristics is capable to satisfy the above described requirements.

As cam actuator was chosen triple mechanism with a target pusher. For replacement of a sliding friction with friction stagger and reduction of wear of a cam in the scheme of the mechanism the additional part – a roller is included. Mobility is local in this kinematical pair and does not change transfer functions of the mechanism. Given mechanism of the cam actuator is intended for transformation of linear motion of a cam to back and forth motion of the pusher. Thus in the executive mechanism of the given type, it is possible to realize transformation of movement under the complex law. One of the important advantages of the cam actuator is the opportunity of maintenance of the exact stops of the output. At the designing the given mechanism in structure of LVAD it is necessary to consider its heat-power characteristics, as at work of a drive a thermal emission is inevitable, but it does not reach so high values to lead to the heating of the body because motor works in a mode without reverse. This basic advantage of the offered design with a cam in comparison with earlier drive of the LVAD on the basis of roller-screw mechanism was developed in Vladimir State University.

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SPECIAL HEALTH FEATURES OF PARENTS AND PRIMOGENITORS OF THE GIRLS WITH MENSTRUAL FUNCTION FORMATION INFRINGEMENT IN THEIR PUBERTY.

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The revealing of infringements of girls-teenagers' menstrual reproductive function formation is based on the definition of the formation risk factors of their reproductive function, connected with their mothers' and close relatives' health. The genetic aspects of the menstrual function infringements, connected with the gene program deviations of reproductive function of many generations allow to assume the girls-teenagers' reproductive function character.

The purpose of our work was to reveal special health features of parents and primogenitors of the girls with menstrual function formation infringement in their puberty. The estimation of anamnestic and clinical characteristics of 232 married couples of mothers and the fathers having daughters with the menstrual function formation infringement, and also 232 married couples of grandmothers and grandfathers on the maternal side has been carried out.

Parents (116) and primogenitors (116) of 15-18-year-old girls with the menstrual function formation infringement in their puberty formed the basic group. Married couples of parents (116) and primogenitors (116) of girls with physiological puberty formed the comparison group. While estimating the distinctions Student t-criterion was used.

In the basic group of mothers the significant increase of somatic and gynecologic diseases has been revealed, the last having appeared in their reproductive age. Authentically the diseases of ENT-organs 90 (77,6 %), cardiovascular 97 (83,6 %), endocrine 99 (85,3 %), digestive 64 (55,2 %) and respiratory 34 (29,3 %) systems occurred more often. At mothers in the comparison group the diseases of these systems occurred accordingly 29 (25,0 %), 46 (39,7 %), 33 (28,4 %), 19 (16,4 %), 13 (11,2 %). From gynecologic diseases in the basic group of mothers authentically more often the background disease of uterine cervix 67 (57,8 %), menstrual period infringements 46 (39,7 %), inflammatory true pelvis diseases 56 (48,3 %) and benign new growths of uterus and ovaries 40 (34,5 %) occurred. At mothers having daughters with physiological puberty the diseases occurred accordingly 42 (36,2 %), 20 (17,2 %), 32 (27,6 %) and 11 (9,5 %).

In the group of fathers having daughters with the menstrual function formation infringement, the authentic increase of diseases of bronchi-pulmonary system 53 (45,7 %) has been noted, in the comparison group these diseases being noted less often 36 (31,0 %). Grandmothers of the basic group suffered authentically more often from the diseases of cardiovascular 94 (81,0 %), endocrine 77 (66,4 %), digestive 55 (47,4 %) systems, whereas grandmothers of the comparison group suffered from those accordingly 26 (22,4 %), 28 (24,1 %), 26 (22,4 %). The grandmothers having grand daughters with the menstrual function formation infringement, authentically more often had benign and malignant new growths of reproductive organs 44 (37,9 %), in the comparison group - accordingly 12 (10,3 %). Grandfathers of the basic group suffered authentically more often from the diseases of cardiovascular 90 (77,6 %), bronchi-pulmonary 60 (51,7 %) and nervous 39 (33,6 %) systems, whereas in the comparison group grandfathers suffered from the same diseases twice as less often 45 (38,8 %), 39 (33,6 %), 15 (12,9 %) ($p < 0,05$).

Thus, somatic and reproductive diseases of girls' parents and primogenitors are a negative background for their reproductive function formation. The realization of the gene

program is shown in the immune and homeostatic trouble in parents' and primogenitors' generations and defines girls' menstrual function formation infringements in their puberty.

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THE IMPROVEMENT OF PHARMACEUTICAL ASSISTANCE FOR THE EMPLOYEES, WORKING UNDER ROTATIONAL TEAM METHOD

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Sakhalin Region is the single insular region in Russia, comprising Sakhalin Island, Moneron Island and Tyuleniy Island located nearby, moreover there are two chains of the Kuril Islands. The profitable geographical location of Sakhalin, its neighborhood to the highly developed countries of Asian-Pacific region, its wealthy resources contribute to the dynamic external-economic relations development. Oil and gas reserves offshore Sakhalin became an important element of the economical development of Sakhalin island, adjoining regions of Russia and the whole Asian-Pacific region as well. Nowadays Sakhalin oil and gas projects (Sakhalin- 1, Sakhalin- 2, Sakhalin- 5) are the most large-scale investment projects in Russia. Oil and gas projects development is implemented in the geographically remote area, in severe climate conditions and in the zone of high seismic activity. All this conditions require the application of leading-edge technologies and pioneering development in various fields of national economy, moreover human recourses attraction is also an important element. The quantity of the economically active population amounted to 302.000 people by the end of June 2006. In accordance with employment department statistics, the level of unemployment in Sakhalin region is the lowest among the Far East regions and totals 2,0 %(on the average in Russia – 2,7%). The demand of personnel equaled to 35.300 people in 2006. Judging by the Sakhalin statistics the international migration balance was positive. During January-June 2006, 11627 foreigners were engaged to work to Sakhalin region with the help of migration service, and the amount of employees was twice as bigger then it was in 2005. The labor power was engaged from 68 countries (Australia – 117, Great Britain – 297, India – 83, Indonesia – 98, China – 813, Malaysia – 134, Nepal – 77, The USA – 514, Philippines – 1038, Turkey – 4955, Korea – 1063, Japan – 96, Thailand – 310, France – 71, CIS countries – 1483 people). Judging by this, the major part of engaged foreign labor power in Sakhalin region falls on Turkey (42,6%), Korea (9,1%) and Philippines (8,9%).

Therefore the problem of pharmaceutical assistance improvement for the employees of such companies as Exxon Mobil, Shell (Sakhalin Energy), BP, Nippon Steel, Saipem UK, Aker Marine Contractors, Transocean, Fluor Daniel, Lukoil, Rosneft (Elvary), Starstroi and others, working under rotational team method on the remote areas has gained big actuality, and stipulated timing and reasonableness of this research. The aim of the research is the development of complex medico-social program of medicamentary supply and improvement of pharmaceutical assistance to the migrants of Sakhalin Region.

CJSC "AEA International (Sakhalin)" (hereafter "AEA Int") – takes the first place among the leading organization of the Far East region in provision of medical and pharmaceutical services on the remote job sites of the companies working in frames of oil and gas projects internationally. Given high demands making to the safety technique, danger in terms of being injured during exploration works implementation, cleansing of territories from explosion-hazard units by sapper teams during assembly operations during part-time residence camps construction along the pipeline laying route, significant remoteness of construction objects from stationary medical institutions, contractor companies have a necessity to obtain urgent and acute medical

assistance in “AEA Int”. The provision of high quality medical assistance is not possible without pharmaceutical support nowadays. The pharmacy of the company provides the medications to the 20 medical facilities, situated in remote regions (onshore as well as on the 4 oil rigs offshore) and on the ships. Therefore the main function of the pharmacy is to supply the pharmaceutical assistance to the employees working in different fields in frames of projects.

On the first stage of the research, regional features of external-economic performance, integration processes and many other regional factors, based on the systematic approach and contemporary methods of economical model building were analyzed. The most significant from them are medico-demographical features (based on the results of ranking Kr = 0,82), which affect the MP (medicine provision) process. The analysis of the Sakhalin Region population disease incidence during 2005-2006 showed that the blood circulation diseases take the first place among other diseases (53,5%), comprising heart related diseases, casualties of food poisoning and injuries (18,8%), the third place is after neoplasms (11%). The analysis of the disease incidence is an essential part of the research in the MP process, because this factor forms assortment and goods policy of the pharmacy.

The second stage implies the development and introduction of step by step accounting, which gives an excellent opportunity of taking a note of high costs, related to remoteness of the objects, and at second, to produce the analysis of profitability, separated medications and assortment of production in whole. There is an economico-mathematical model of step by step accounting of medical provision (4 formulas):

$$CM1 = \sum_{i=1}^{n} (Vi \times Pi - VCi) \quad (1)$$

$$CM2 = \sum_{i=1}^{n} (Vi \times Pi - VCi - FCj) \quad (2)$$

$$CM3 = \sum_{j=1}^{m} (CM2j - FCj) \quad (3)$$

$$CM3 = \sum_{j=1}^{m} (CM2j - FCj) - FC] \quad (4)$$

Where: CM1- the (ruble) coverage of the separated assortment units in frames of pharmaceutical production (PP); CM2-the (ruble) coverage of the separated kinds of PP; CM3- the (ruble) coverage of the separated assortment groups of pharmaceutical goods; I- the result of the enterprise performance (profit and damage); V- the volume of the realization of PP; P- price factor; VC- variable costs; FC- fixed cost; I- kind of production in assortment of enterprise, I=I……n, where n is the number of PP; j-the kind of assortment group of the enterprise, I= I……..m, where m is the number of assortment PP group. With the help of this methodic the following results were collected: the highest points (589) were given to the group of medications, helping the patients having heart-related diseases, where the leaders were Actilyze, Cozaar, Liprimar; the second place (517 points) was taken by the medications helping if a patient has infective diseases, the leaders in this group became Ciprobay,Klacid,Augmentin, the third place(432) was after the group of vitamins with Centrum, Vitrum, Upsavit C; the fourth place with 368 points was taken by group of vaccine with Avaxim, Vaxigrip, FSME vaccination; the fifth place with 273 points is taken by the group of Nonsteroidal Anti-inflammatory drugs with Celebrex, Ibuprofen, Diclofenac.The group of opioid analgesics is taking the sixth place with 117 points, because those medications should be supplied to the medical facilities on the remote objects for the providing of urgent and acute first aid. The method of step-by-step accounting was also applied for the development of regional “Vaccinal prevention”, “Avian flu” and others.

The complex medico-social program which included: verification of the required list of medications, expendable medicational materials; development of actions algorithm, directed to the quality of provision and optimization of pharmaceutical performance on every stage when the medications are delivered, kept and sold with the adherence of international standards of ISOS and RF legislation; the development of methodic instructions about the work of mobile medical teams on the construction objects working under

offshore projects on the territory of Sakhalin region.

Thus, due to research work the methodic approaches were improved in the area of providing the pharmaceutical assistance for the employees (including the assistance to the migrants), working under rotational team method in the frames of Sakhalin 1, 2, 5 projects. The introduction of the mentioned recommendations about the mobile medical teams work regime (the act of introduction №2586 dated 30.12.2004) enabled to work out the complex medico-social program of MP of the migrants of Sakhalin region and provide the pharmaceutical assistance in accordance with the international standards.

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APOPTOSIS AND LOCAL IMMUNITY OF CHRONIC HCV-INFECTION

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The programmed cell death takes part in the body development regulates the number of the cells in the tissue and is the main thing of many immune reactions. Understanding of activation processes and apoptosis realigation in a cell is of great clinical importance in case of virus hepatitis.

The aim of our inrestigation is to evaluate the interrelations between the apoptosis condition and the cytokine architectonics in the target-organ-the liver in case of HCV-infection.

Investigation results indicate of the increased number of CD95+ cells in supernatants of the liver bioptates in patients with chronic HCV-infection. It shows the considerable role of the mechanisms of the programmed death cell in the pathogenesis of chronic HCV-infection. Their apoptosic activity lowering is of importance in the progress of necroinflamotory liver injuries and may testify to the strengthening of the immune system disfunction when the disease grows progressively worse. The increased cell level having apoptosis marker CD95+ in supernatants of the liver bioptates correlales with high level of the local cytokines TNF-a ($r=0,34$; $p<0,01$), IL-1a ($r=0,56$; $p<0,01$) and IL-10 ($r=0,66$; $p<0,05$) and it is possible to indicate HCV us age of hepatocytes apoptosis mechanism for its survival in a hostis organism. And with the increase of the hystological activity and the liver fibrosis TNF-a antiviral acticity in HCV-infection persistencia conditions is insufficient and it may be for example due to the increased secretion of the solvable receptors connecting TNF-a. Direct correlation between local CD95+ cell content and IL-4 ($r=0,32$), IL-12p40 ($r=0,65$) and IL-12p70 ($r=0,21$) cytokine concentration has been revealed in supernatants of hepatobioptates howerer their differences were not accurate. Negative correlation between IFN-a, IL-2 local cytokines concentration and the number of proapoptosic CD95+ cells ($r=0,5$; $p<0,01$ and $r=0,25$; $p<0,05$) accordingly that may as well speak on the lowering of the antiviral defence on the organ's level with the apoptosic mechanisms increase which helps persistencia of HCV- infection.

Thus the disturbance of cytokine balance leads to the apoptosic hepatocytes death and it is of great importance in the liver cell injury in case of chronic HCV-infection.

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Shot report

A ROLE OF NO-ERGIC MECHANISMS AND APOPTOSIS IN THE CONTROL PROCESS OF PROLIFERATIVE ACTIVITY OF EPITHELIAL CELLS

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The basis of the organized research is the fact that the process of age-dependant cell depletion is genetically determined and has the same cytological and biochemical evidences in different organs and tissues and can be defined as the physiological preset necrocytosis. The abnormality of the physiological equation between the division and the death of cells is a base not only of tumorous but also some nonneoplastic diseases. The base of degenerative diseases is probably a dysfunction of the apoptosis system. The influence on the program of necrocytosis or proliferative activity is one of the perspective directions of the conservative medical treatment. We did not manage to find out the exhaustive information about no-ergic mechanisms of influence on the apoptosis processes and the growth of activity regenerative potential of the integumentary epithelial colony-forming.

The high concentration of nitrogen oxide (NO) arises because of the following factors:

- in condition of phologistic and immune reactions in epithelial mucous plate and epidermis;
- iNOS synthesis activation in cells.

The role of nitrogen oxide in apoptosis mechanisms comes to the cytotoxic influence of a molecule on a target. Mitochondria play a great role of an acceptor of nitrogen acid in the induction of apoptosis due to the high content of the ferrous sulphide protein ferrous sulphide protein. The poisonous effect appears in suppression of mitochondrial enzymes that leads to the decreasing of production of adenosine triphosphate and ferments, taking part in the process of DNA replication, and also direct damage of DNA.

The deactivating influence of nitrogen oxide on apoptosis is realized through cysteine proteinases by way of nitrilasing of thiol groups of cysteine proteinases.

In ontogenesis and when the reaction to the damage the program of necrocytosis starts the single-type molecular mechanism, however the intensity of the process is connected with various cytotoxic and tissue protective effects of nitrogen oxide. The carried out analysis of NOS activity in epithelial layers of mucosae and epidermis at all the stages of human ontogenesis showed that the physiological NO synthase certainly plays a great role, as an inductor of the differentiation process, the growth and specialization of epithelial cells. As we found the growth of apoptotic index is combined with the positive reaction to iNOS in epithelial cells. Likewise the activity of NADPH-diaphorase is rising, representing the total content of constitutive and inducible NOS.

The change of strictly programmed phases of elective death of cells, caused by apoptosis, correlates with the development of NOS activity in epithelial layer of mucosae and epidermis.

The further analysis of the role of nitrogen oxide, as an active partaker of biochemical and proliferative process in a cell with its unique ability to induce and inhibit apoptosis, is necessary.

JOINT CROPS OF THE WINTER WHEAT WITH MEDICAGO (LUCERNE) - THE FUTURE OF PLANT GROWING

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Recently in different regions of Russia the process of mass passing to adaptive plant growing has begun. The industrial managers understand this passing in different ways, not completely understand the main idea and methods of intensification of adaptive plant growing. A.A.Zhuchenko (2004) a member of the Academy says: "The strategy of intensification of adaptive plant growing is directed towards the enlargement of productional but also environment improvable function of agro ecosystems and agro landscapes."

In the Rostov Region the amount and quality of the crop basically depends on the nature's caprice, therefore, while inculcation of adaptive plant growing in agricultural practice, it is necessary to pay more attention to the reduction of risk degree while getting high and stable crops of the main cereal in the Region – the winter wheat. And there is a necessity to select sorts adaptive in concrete conditions of the growing process, and mostly to develop technologies of cropping according to the special features of forming of crop rotation in modern conditions, with limited amount of cultivated cropper.

This strategy of adaptable cropper is based on the fact that recently most of the soil quality is practically used in the various Regions of Russia. The crop is got only due to the nutrients in the soil, the fertilizer is applied on the limited acres, and in those farms which have protectors or belong to the firms occupied with implementation of chemical means of plant protection or fertilizer in the territory of Russia.

Some economic executives misunderstand the notion of D.N.Pryanishnikov, who marked a special role of fertilizer and getting heavy crop. He wrote: "The heavier is the harvest the less is getting of it using only nutrients from the soil itself and the greater is the importance of fertilizer for providing the crop with all necessary amount of nutrients." The disparity of farm and fertilizer prices make bare proprietors to cultivate crop not looking after safety without mentioning of the growth of the soil fertility for the future generation.

The territory of the Rostov Region is in a certain degree an undulating plain at an elevation from 30 m. till 300 above the sea. The highest area is located on the north-east, where the outskirts of the Don Ridge run, and more than a half of the farm fields are located on the slopes of different steepness and are liable to the wind and water erosion.

The growth of the yield of the cultivated crops must be accompanied by the rising of soil capabilities. But the biggest obstacle to the future development of the agricultural manufacture is a soil erosion. The eroded soils are less rich than the soils without erosion; hereupon the yield of crops here is dropped by 12-62 %. In the Rostov Region the square of such area is about 2 million ha; more than 4 million ha is in urgent need of protection from the erosion.

One of the fundamental elements of agro technologies in dry conditions of the Rostov Region is a complete fallow – the best precursor of the winter crops. It is also known that the complete fallow has some material weaknesses. That is why there have been many discussions about the optimal square of the complete fallows in the structure of ploughed fields among the specialists of agriculture. But the complete fallow has an effect only while qualitative cultivation of the soil and technical measures, which provide getting high and stable crops during all the rotation of crops.

The intensive water erosions are observed at the Don River in winter, spring and summer

periods. Therefore the autumn fallow erosion processes have been occurring from the moment of the primary processing and till the dropping of winter crops.

One of the most effective ways to stop the snow and protect the soil from the erosion is using the Medicago hedges. In winter period the Medicago facilitates detention and even distribution of the snow in the field, and better wintering of the winter crops and water collection. The soil itself reinforced with the coulisse plant roots and mulched with plant fragments, better protected from the water and wind erosion, and also from the insolation in the period of fallowing.

Using the Medicago hedges in fallows is a promising method of crop yield rising. The Medicago is drought-resistant and able to weather the 30 degree frost in the hard non-snowy winters. Its root takes phosphorous, calcium and other elements from the deep soils. These elements are involved in the process of structural soil outfit generating, accumulate in the plough-layer and make feeding schedule better. The Medicago contributes greatly to soil detachment, makes lower soil discharge and slows down the process of the plowing layer salting.

The Medicago uses nodulating plants for nitrogen fixation. That was proved that the roots and afterharvesting residues of this cropper collect 100-150 kg and more nitrogen per hectare that keeps in scale with 4-6 of nitrogen fertilizer.

We worked out, put to an evaluation test in practice and applied in industry a new way of using the http://www.multitran.ru/c/m.exe?t=1571020_1_ 2legume grasses (Medicago Varia) in the screen fallows for the production of cereal grain of the winter wheat and soil conservation (patent № 2260929 of the RF)

The researches have been conducted in the fields of the Don Cultivar experimental study center called *Don State Agrarian University* since *2000.*

The Medicago is used for creating a hedge-mulching fallow. It must be overdrilled by the row-crop planter SUPN-8 (or other model) between the spring barley; the spacing – 70 cm and seeding rate up to 2,5-2,8 kg/ha. Thus, compared with the traditional Medicago undersow, there is a significant economy of bean culture seeds. After spring barley gathering the Medicago overwinters, then in spring the intercultivation is organized and in autumn the winter wheat is sowed.

On an average over the years of survey, in the second year the harvest of the Medicago Varia herbage was 9,2 ton/ha, roots – 2,0 ton/ha, crop remains (остатки) – 1,2 ton/ha. The share of roots of the crop remains is about 65-70%. The most effective Medicago root system developed in the first year, in the second year – the field mass.

The organics are admitted into the soil after the bean culture harvesting and has great importance both for supplying the soil with fresh energy material and fertilizer elements. It all goes to show that there are favourable backgrounds of having positive balance of organics and fertilizer elements in the soil. The amount of the nutrients in the soil depends on the percentage of these elements. We have found out the chemical composition of the Medicago Varia plant remains (%): N - 2,34; P_2O_5 - 0,29 and K_2O - 1,28.

The 2002 and 2004 years were wet and favorable for collecting fertilizer elements in the plant remains, the NPK content here was for Medicago Varia - 82,5-98,3; 9,7-12,2; 50,0-51,3 kg/ha. In dry 2003 NPK content decreased – 35,2; 5,8; 26,9 kg/ha properly. According to our research the average content of the NPK in the plant remains of the Medicago Varia is 76, 9, 42 kg.

The intense occurrence of the water erosion on the Don River is observed in winter, spring and summer. That's why the erosion processes on the autumn fallow have been proceeding since the moment of the main cultivation and until the winter crops dropping. The coulisse fallow in this regard is more preferred than the autumn fallow. The value of the soil loss on the various fallows essentially differs on the slope areas of $3,8^0$.

The scientific Institutions found out the annual losses of the melt waters are 50-60 bln m^3.

If it is possible to stop even a half of them in the fields, that will give a possibility to increase the whole yield of the crops about 8-10 Mio ton.

Each 10 mm of the melt waters (100 ton), saved and rationally used; there are 2 extra centner of the winter crops and 1 centner of the spring crops.

The Medicago Varia sewed across the slope, further formation of more water-stable structure and better moisture absorption. While soil preparation, the erosion preventive bunds are conforming – the prototype of the swathing in the complete fallows.

The more stable element is a complete fallow, in which the erosion has been since the main cultivation and till the dropping of the winter crops. So, the complete fallow causes the total soil loss of 154 m^3/ha in the period of 3 years (2003-2005), and the Medicago fallow was 7 times less.

According to the period of the fallowing the various rainfalls precipitated during the years of research. The duration of the fallowing period also depended on the fallows under study. Over the period of the research this duration was: in the complete fallow – 164 days, in the coulisse fallow -101 days. It is necessary to mark the Medicago Varia ripens in 63-72 days since the re-vegetation. The amount of the loss water, considering the past precipitation in the complete fallow, over the period of the fallowing was 288 mm that is 105-107 mm higher than in the coulisse fallow. However, the certain advantage of the complete fallow over the other fallows is that by the moment of the winter wheat dropping there is more moistness than after the coulisse fallow. In the complete fallow the amount of the past precipitation over the period of the fallowing is lost as the evaporation and the surface discharge (поверхностный сток), as the part of the moistness collected over the autumn and winter period. The moister, lost in the complete fallow during the fallowing, is efficiently used by the Medicago in the coulisse fallow for the yield formation.

In autumn the winter wheat is sewed according to the seeding rate, recommended for the breed and the area of cultivation. The winter wheat is sewed at an angle of 15-30 degrees toward the Medicago rows. The winter wheat and the Medicago overwinter and in spring the Medicago contributes to the decreasing of the erosion processes caused by the snowmelt. The soil loss in the winter wheat dropping in the complete fallow was 16-20 m^3/ha, and in the coulisse fallow – 3-4 m^3/ha.

The structure is also an important characteristic of the soil physical state. It determines the favorable plowing layer of the soil, its water, physical-mathematical and technological features.

By the moment of the winter wheat dropping the various soil structures have been forming, depending on the type of the fallow. In the complete fallow the soil is breaking cause of numerous cultivation and shower rains that leads to the decreasing of the valuable elements (10-0.25 mm). The soil is being structured, i.e. the amount of the water and wind stable aggregates (агрегатов) is decreasing. Over the period of research in the complete fallow the aggregates (in size down to >1 mm in the layer of 0-5 cm and to >0,25 in the layer of 0-20 cm) were properly 45,3 and 36,5 %. In the coulisse fallow (кулисный пар) fallow the amount of the aggregates (in size down to >1 mm in the layer of 0-5 cm and to >0,25 in the layer of 0-20 cm) increased 1,6 and 1,8 times.

The largest containing of the water stable aggregates in the soil was in the variants of the coulisse fallow (кулисный пар), that provides (обеспечивает) the growth of the infiltration of water up to 2,96 m/min.

By the time of the winter wheat harvesting the Medicago has begun to blossom, and on some side twigs the seedpods are forming. It is necessary to mark the essential condition of harvesting of the binary crop is a separate method. The harvester-shredder should be used for shredding and dispersion of the chaff and the Medicago – thus creating the mulch cover that protects the soil from the overheat and water loss. The crop yield of the winter wheat in the coulisse and mulch fallow over the years 2001-2005 was 40,3 hundreds kilograms per hectare. That is lower than the crop yield in the complete fallow – 42,7 centner per ha, but the great positive side is that there is more than 3 months before the frost, and that is enough for the Medicago to grow, blossom and bear. So we get the grain of the winter wheat and also according to the aim of using – the Medicago herbage and corns. Since 2001 and until 2005 the harvest of the Medicago corns was from 0,8 and to 1,6 ha

(the middle yield of the Medicago – 1,2 centner per ha) in the year of the winter wheat harvesting. It is easy to count up that the good farmer will get about 8000 extra rubles above the sum of the price 8000 rubles per 1 ton of the Medicago corns.

The quality of the wheat fibrin has a great importance in the feeding. The high quality of the fibrin determines the high quality of the flour for baking process. On the average over the years of research the high containing of the raw fibrin was found in the coulisse fallow – 32,3%, in the complete fallow – 30,7%. And the greatest vitreousness was in the coulisse fallow – 62%, that is 2 % more than in the complete fallow.

The other important corn quality level is a cup weight, characterizing the yield of flour and the plumpness. The higher cup weight was formed in the coulisse fallow (764g/l).

Thus, the coulisse fallow as the complete fallow furthers getting the winter wheat corns of high quality and even is better.

On the farms with developed animal agriculture the Medicago Varia is necessary to be sewed with the winter triticale and winter barley in the coulisse and mulch fallow in order to conserve the forage.

Materials of the Conferences

GENETIC EVALUATION OF BULLS ON MASTITIS RESISTANCE BY MEANS OF LINEAR STATISTIC MODELS

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Accuracy of animal breeding value (BV) is the actual problem of selection. The best linear unbiased prognosis method (BLUP) is applied for the estimation of BV in the countries with developed animal breeding PC software. Advantages of the method are: a calculation of environmental factors influencing (it may dislodge a true estimation of an animal genotype) and relatives information. The BLUP method is approving in the Russian cattle breeding for the BV estimation of production traits. However dairy cattle of all Russian herds requires in technological traits improvement also, including mastitis resistance increase. As the mastitis is one of widespread and expensive illnesses of dairy cows. The frequency of the disease varies within the range of 12-40 % up to 50-80 % [2]. The losses from one case of mastitis are equivalent to the cost of 400-470 kg of milk [3].

The purpose of our research is the BLUP evaluation of bulls-sires genotypes on daughters mastitis resistance. The research was conducted on the data of first three lactations of Ayrshire cows (daughters of 40 sires, 1983-1998 years of calving, 5145 lactations totally). Resistance-susceptibility of cows to mastitis were estimated on score scale, carried out with application of logarithmic transformation (LnX+3,4) [1]. The score for healthy cows equals 3,00, for mastitis suspect cows - varies from 3,17 up to 6,10, for mastitis cows - from 6,11 up to 26,00. reeding value of bulls (BV) was evaluated by BLUP.

The statistical model included fixed effects of year, month of calving, milk yield, weight, period from calving to insemination and intensity of milk ejection of daughters.

The mean score for mastitis varied from 3,00 for the daughters of the best bull up to 6,59 of inferior one. BV estimations of sires varied from -0,87 for the best bull up to +1,48 score for the inferior bull. Reliability of BV estimations of different bulls was from 7,4 to 91,0 %. Genetic repeatability of BV estimations was at the high level (r_g=0,683…0,706).

Our analyses has shown: it is possible to increase the effect of selection of more mastitis resistance genotypes on 16-40 %, using sires, genetically evaluated on mastitis score by BLUP [4]. So, it is necessary to conduct a mastitis resistance trait in electronic pedigrees of cattle (both males and females) in all Russian dairy herds. Such approach allows one to predict a complex breeding value of cattle.

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Materials of the Conferences

THE ANALYSIS OF VARIANTS OF INVERTER CONTROL FOR SECONDARY POWER SUPPLIES

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Recently the push-pull bridge and half-bridge inverters are being used more and more in secondary power supplies (SPS) within the limits of power from the dozen of W to a few kW, for example, in electronic welding machine, single-phase plasmatron, electronic voltage stabilizer and so on.

The bridge inverters include Transistor Bridge in the power part; this bridge is shunted with bypass Diode Bridge and connected by the DC diagonal to the mains rectifier, and by the AC diagonal to the load [1]. The half-bridge inverters have one half-bridge consisting of two transistors and two bypass diodes, this half bridge is the same as the half-bridge of the bridge transistor. The other half-bridge is formed by 2 condensers connected in series; the load is put in between the point of these 2 condensers and the point of the first half-bridge.

The feature of the half-bridge circuits is a principal lack of steady component in the load diagonal that makes this circuit more preferable for the transformer load.

The second feature of the half-bridge is that most of the load range is functioning at the constant power; the energy of condensers while constant voltage of the power supply:

$$W = \frac{CU^2}{2} = const .$$

Hence it appears that the half-bridge inverter is ideally suited for the electro welding in the air, i.e. at the constant arc power.

The mains rectifiers as in the push pull inverters as in the known single-ended inverter of the examined SPS at the high power under 1 kW – it is an ordinary diode transistor bridge.

The controllability is necessary for the inrush current limitation, while the smoothing condenser charging at the output of the mains rectifier.

So, the common structure of the SPS contains two adjustable (regulated) units: the mains rectifier and the inverter. Therefore, there are three variants of forming SPS control circuit:

1. The concurrent control over the mains rectifier (phase) and inverter – the pulse-width modulation (PWM).
2. The control only by the inverter (the rectifier is controlled only in case of starting and short control).
3. The control only by the rectifier.

The controlling systems for the push-pull bridge and half-bridge inverters were developed on the level of the standard (sample) microcircuits, where the outputs are conjugated (coupled) with the middle driver, or directly with power optoelectronic modules. The optoelectronic bypass is necessary because the PWM driving pulse relative duration is changing, and the galvanic separation become practically impossible because of the pulse transformer; at the control area it is very difficult to provide the negative bias at the power transistors of the inverter.

Note that for example the price of a bipolar transistor IRG4 with commutating power up to 200 W is about 5 dollars, at the same time the optoelectronic module with the same output capacity costs more than 40 dollars, i.e. the optoelectronic modules in the controlled inverters mostly determine the price of all the inverter.

In the third case (the control only by the rectifier), there is a possibility for direct manipulation of the power transistors realized by the self oscillator, that makes the inverter more simple and not so expensive, and the SPS on the whole[2]. The review of this case is the object of the article.

The common SPS circuit with uncontrolled inverter contains the net half controlled mains rectifier the mains rectifier control system and the bridge inverter, for example, bipolar-fet integrated circuit. The inverter control system consists of the self oscillator with the output matching transformer, self-saturating reactors (by the number of control channels) and the

control pulse formers, also by the number of control channels.

The inverter is functioning in the following manner.

The oscillator transmits the voltage of the intended frequency through the matching transistor in the control current of the transistor inverter. The transformer scales the potential difference (voltage) to the desired value necessary for manipulating of the chosen type of transistors. Each control channel has a saturated reactor. When the impulse from the matching transformer has a direct polarity, i.e. opens transistor, the opening happens only after the saturation of the reactor, because the magnetizing current creates the voltage drop less than the stabilizing voltage of the stabilitron. When the impulse has a reversed polarity, the power transistor gets the negative voltage even while the saturated reactor, because the stabilitron is connected in the direction of the back impulse. Let us remark here that if we chose the power transistor as the bipolar transistor, than there is no need of stabilitron, because the minimum voltage while the opening of these transistors no less than 3 volts. According to the chosen resistors resistance the time of reactor saturating by the back impulse will be within the following limits: $t_в$ « t < 0,5 T, where T is the period of the oscillator voltage. In this case the reactor voltage integrals were the same for the both half-waves. By the moment of opening of the next diagonal (bias) pair of transistors, the pairs which were at the back-bias (negative) voltage. This period should be longer that the recovery period of the turnoff characteristics of the used power transistors. Particularly the bipolar transistors IRG4 have the total turn-off and turn-on period about 0,5 microseconds, and the control voltage (gate-source) about 15 volts that let us to count the reactors by the formula:

$$U = 4{,}44 \cdot f \cdot B \cdot S \cdot W,$$

where U = 15 B, f = (50÷100) kHz (usual frequency of inverters, for example, in electronic welder transformers), $t \approx 0{,}5^{-6}$ c, $B \approx$ (0,2 ÷ 0,4) T S – for ferrite cores and W – turn number of the choke coil.

The evaluation shows that the adequate $t_в$ provides the core $S \approx (5 \div 7)$ mm^2 with turn number W≈15.

Thus, the adequate $t_в$ is achieved with 4 pigmy ferrites, and the power part of inverter become simpler and less expensive.

According to the $t_в$ value it follows that even at the frequency of 100 kHz the relative pulse duration of the on-load voltage is about 0,9 (figure 6). It is obvious that if the direct current load is the same as in the electronic welding machines than the rectified voltage filter becomes rather lighter than while using the PWM method.

At the same time this method has a disadvantage: the speed of operation realized with the rectifier is much lower than while operating with the PWM inverter load.

However, as the practice of engineering and production of the electric welding machines shows, the speed of the rectifier control system is enough for stabilizing of the electric arc; and in this case it is easier to provide the influence of selective protection of the inverter on the active oscillator as it is realized in the well-known engineering.

CONCLUSION

Most of the secondary power supplies (SPS) with controlled mains rectifier and the push-pull inverter control and regulate the output parameters: phase – with the mains rectifier and the pulse-duration, and the optoelectronic transistor module as the power switching sells, which provide the galvanic separation and connection with the output of control system.

The SPS controlled only by the rectifier is suggested in the article. That gives a chance to desist from the use of optoelectronic modules and to control the power transistors by direct use of the active oscillator and also to simplify filtration of the rectified current for the DC load.

The given decision totally makes the SPS simpler and less expensive, and can be recommended for the loads successfully controlled with the mains rectifier, for example for the electronic welding machines.

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Shot report

USE OF ELECTRONIC AND MICROGRAPHIC TECHNOLOGIES FOR PROCESSING AND PRESERVATION OF THE INDUSTRIAL DOCUMENTATION

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The major role in realization of any production process belongs to design, technological, normative and technical, operation, repair and other industrial documentation. The loss of the specified industrial documents inevitably leads to the output termination.

Despite of the accepted industrial documentation preservation measures, there is always a risk of its irrevocable loss because of fires, technogenic accidents, natural disasters, acts of terrorism, military actions and other extreme situations.

To solve the problem of fast completion of the documentation necessary for manufacturing of the important for the state needs production, destroyed, damaged or physically inaccessible in conditions of wartime or extreme situations effectively is possible by means of preliminary creation and reliable preservation of an insurance fund of the industrial documentation.

The documentation insurance fund is a set of the sequential files of backup copiers of the documents made on compact carriers, kept in special storehouses providing their reliable protection from destruction and loss in conditions of extreme situations and wartime.

Proceeding from the predestination of the documentation insurance fund, the technological processes applied during its creation, preservation and use, should provide:

- the authentic compact long- term storage carrier record of the documentary information presented in the analog and digital form;
- the long-term preservation of the documentary information loss- and distortion-free;
- the high stability opposite external adverse influences;
- the high degree of protection from not authorized access, distortions and deliberate destruction of the documentary information;
- the stability of used technologies for a long period of time;
- the reliable and operative reproduction of the kept documentation loss- and distortion-free in any time interval from the moment of its being introduced into the insurance fund;
- the opportunity of remote telecommunication access to the insurance documentation kept.

The integrated (hybrid) electronic-micrographic industrial documentation processing and storage technologies meet the specified requirements most fully. The complex use of electronic (computer) and micrographic technologies allows to combine effectively the high stability and the long preservation reliability of backup copiers of the documents fixed (recorded) on microfilms in analog human readable form, with the opportunities of operative search, telecommunication access and reproduction of the documents transformed into digital (electronic) form, at various adverse factors of influences.

Basic provisions of electronic and micrographic processing technology, the insurance storage and the use of major industrial documentation, developed in the Scientific Research Institute of Reprography consist of the following:

1. To create industrial documentation insurance funds the following documents are to be subjected to electronic and micrographic processing:
   - the alphanumeric and graphic documents represented in black-and-white and color version on paper carriers;
   - the alphanumeric and graphic documents represented in black-and-white and color version in an electronic form on machine data carriers;
   - the documents containing computer (EDPM) programs and recorded on machine information carriers.
2. Backup copiers of all kinds of documents (excepting program ones) are made in the form of rolled 35 mm microfilms represented on

black-and-white silver-gelatin films with the optical resolution of 600-700 lines per mm. The specified microfilms provide complete safety of the documentary information within 100 and more years, have high stability opposite external adverse influences, do not allow to make not authorized changes and deliberate destruction of the information, can confirm legal validity of the authenticity of the information of the lost documents.

3. Backup copiers of the documents represented in black-and-white version on paper carriers, are made by means of their optical microfilming on highly resolving film-making cameras (microfilming devices).

4.Backup copiers of black-and-white alphanumeric and graphic documents represented in an electronic (digital) version on machine data carriers, are made by means of their computer microfilming on laser micrographic plotter (COM-system), having the optical resolution not less than 7,5 thousand pixels per inch. Thus, for computer microfilming of the complete set of documents from the files of electronic copies of separate documents on a computer an electronic version of a microfilm of the complete set of documents, which is then recorded in the alphanumeric and graphic form on a backup microfilm, is formed.

5. Backup copiers of colored documents represented on paper carriers, are made by means of their color-separated computer microfilming on black-and-white silver-gelatin films. For this purpose, colored documents are scanned with the resolution of 400-600 pixels per inch with the depth of each pixel scanning of 24 bits. Then the color-separating of the digital model of the colored document's image on 3 monochrome colored image models (red, green and blue) is carried out by means of program processing. The monochrome color-separated digital image document models are rasterized (transformed into the binary form) and are recorded by means of laser micrographic plotter (COM-system) on three frames of a black-and-white microfilm which as a whole represent the backup copier of the colored document stored distortion-free for many tens of years.

6. Backup copiers of the programs intended for the computer (EDPM) and delivered on machine data carriers, are made by means of their rerecording on high-quality optical disks which parameters meet the international standards ISO.

7. Microfilms of backup copiers of alphanumeric and graphic industrial documents, and also optical disks containing backup program copiers, are stored(kept) in special storehouses at the temperature of no more than 15 ℃ and relative humidity 50 ± 5 %.

8. The authorized access of users to necessary alphanumeric and graphic documents (complete sets of documents), kept in the insurance fund, is carried out by means of corresponding backup scanning (numbering) of microfilms containing the images of these documents and computer manufacturing of their full-size copies on paper carriers by means of wide format digital plotters.

Thus, the digital plotters' network connection with telecommunication circuits allows to carry out remote reception of documents' copies from the insurance fund.

. 9. The reproduction of colored documents' paper copies from color-separated black-and-white microfilms kept in the insurance fund, is carried out by means of 8-bit scanning of three frames of a microfilm with color-separated images of the document; the colored document's digital image restoration by means of computer combining of the three digital files received as a result of the color-separated microfilm's frames scanning and printing the restored colored document's digital image on a colored digital plotter.

The electronic and micrographic technologies given are approved in the ship-building industry enterprises' design and technological documentation, and also in the colored cartography documentation concerning special hydrogeology.

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CLOSED BY FEEDBACK SYSTEMS THEORY'S PRINCIPLES

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In the material and physical nature the so called "feed back" phenomenon does not exist at all.. It is created artificially in automatic control systems (ACS) of technological processes. For the first time the method is given, that proves the society's and enterprises' economies possess own natural, negatively influencing, positive feedback.

The machine production started in 1765 [1] when a steam machine and the automatic water level controller in the boiler of that steam machine was invented by I.I. Polzunov for the first time. The industry, technological processes and, accordingly, the industry of automatic controolers, as it is impossible to conduct technological processes without them, were developing. Thus, at the end of the 19th century the theory of automatic control systems (ACS) [2] consisting of technological process and a controller developed. After the article of G.V.Shchipanov had been published, [3] contrary to the serious criticism, the theory of invariability in automatics appeared and, since 1958 up to 1982 (VI) All-Union Conferences on the theory of invariability of ACS were held every 4 years. Proportional (P) controllers described by the equation $\Delta c = -Cr x$, with Δc as the controller's outlet change, Cr - the controller's gain coefficient and Δx - the controlled variable change, were large-scale manufactured; proportional-integral (PI) controllers $\Delta c = - Cr(\Delta x + \int \Delta x dt)$; and proportional-integral-differential (PID) controllers $\Delta c = - Cr(\Delta x + \int \Delta x dt + dx/dt)$. The processes were described by linear differential equations. That is why both the controllers and the ACS theory were kept in frames of linear systems capable to work at load variation in the process by 6-8%. Left parts of the processes equations were composed on the experimental data, and the right ones were written in the form of the product f(t) [1]. In them, f(t) is so called "disturbance", being not to the point of the process equation on its functional structure, and [1] – is a unit function of the unknown origin as well. So, both the ACS theory and the controllers remained independent from the symbolic models of technological processes. As the technological processes were developing, the controllers capable to work at load variation up to 100% and a theory making possible to build an ACS on symbolic models of technological processes became required. For this it should have been defined what is what.

Logically, a technological process is a manufacturing process when one or more product streams influence some other one or ones. Thus, a technological process is an interaction of two or more product streams, where the first ones are the material and the second ones – influences on the material, the streams' characteristics being changed. From the controlling point of view the last become regulating parameters, and from mathematical point of view the material, thermal et al. balance equations are symbolic models. As the process outlet is connected with the controller's inlet, the controller's outlet is connected with the inlet of the process (control object), a closed system comes into being. When laid on paper, a previously unknown geometric configuration, called a "***nomogram***"* (pic.1), comes into being, with x – as the value of the circuit/process output parameter, a – the measuring instrument's gain coefficient, m – output values of the measuring system, b_i – the task's structure coefficients, n – the controller's input, u_1 – the controller's output values, f_1 –

loading values. As it is seen from the picture, the nomogram is the basis of invariant systems' construction. The necessary for achieving the invariance condition of values of the controlling parameter at various loading values and the given values of the controlling factor are patently seen in it. This made possible the creation of invariant electronic controllers for galvanic processes for loading change conditions up to 100% [4], [5], [6] and allows one to create invariant ACS for the statics of the process with any forms of non-linearity. The ACS operating mechanism rests on the fact that by the changes in loading on the circuit/process in Δf, an output parameter change (the controlled variable) described by the differential equation occurs. After the transition process, the output variable will be transformed into Δx under the influence of the loading change in Δf. It means that the ***differential equation*** turns into the ***potential equation*****solved relative to Δx after the transition process. For example, on the nomogram (pic.1) the transition from the loading value f_1 to f_2 corresponds to the loading change. To achieve the static invariance in an ACS, the transition of controlling parameter value from $u_1$to u_2 is required. In most cases it is enough. To achieve the absolute ACS invariance, the second (dynamic) condition of invariance, by changing the rate of the controlling parameter's change, must be carried out. These data are given in the report in the 5th Conference [7]. The problem having been left unsolved for 100 years eventually proved to be very simple.

Many centuries ago, philosophers and, at the end of the 19th century, economists noticed that the economies of separate countries and that of the world develop unevenly. Inflations and recessions, which have been called the cyclical results, happened and are still happening. The main point retained is their unknown nature. Building in of the processes/circuits in an enterprise' economy with due regard for special features of economic processes into the nomogram for ACS lead to an overwhelming conclusion, that enterprises' economy possesses own natural positive feedback and it is subject to the theory of not existing in the nature, but artificially created systems, closed by feedback, i. e. the theory of Automatically Controlled Systems.

Nomogram ***– (from Greek = law + gramma) graphic illustration of theoretical or empiric dependencies simplifying practical calculations.

Potential equation – the equation after the parameters' and variables' change.

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Materials of the Conferences

HEAT OSCILLATING EXTRACTION OF RARE EARTH ELEMENTS

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Using classical extraction for separation of chemically similarly elements requires the necessity of construction of cumbrous many-extractors cascades. As a result of this interest to search new alternative extraction methods just becomes greater. Work on development and improvement of separation methods based on nonstationary oscillating extraction has been carried on already more than ten years. Various factors deflecting system from stationary state are used: chemical, electrochemical, temperature and other.

Behavior of extraction system in nonstationary conditions using heat oscillating was investigated. Distribution of rare earth elements between two phases in one extractor and their separation between two extractors under these conditions was studied. Different condition of heat oscillating extraction: different oscillating period and different temperature peaks above normal state (25°C) was used. Optimal conditions for separation of elements with similar chemical properties were found.

Following system with simultaneous presence of two metals was investigated: H_2O – $Nd(NO)_3$ – $Pr(NO)_3$ – tributyl phosphate – kerosene. Determination of metal concentrations was realized using CCD-based spectrophotometers on-line. Modified experimental setup described in [1] was used. The concentration profiles of rare earth in time in aqueous phases and in organic phase showed the dependence of metal's concentration ratio on time. This fact can be used to separate similar elements using heat oscillatory extraction.

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METHODOLOGICAL ASPECTS OF THE STUDY OF THE TEMPERATURE-KINETICS PARAMETERS OF THE F-ELEMENTS' EXTRACTION

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The methodic of the study of non-stationary f-elements' extraction was elaborated. The main methodic aspects of obtaining of the temperature-kinetics parameters were marked out.

The extraction rate constants from the independent experiment with one extractor (Lewis cell) on rare earth elements' (REE) mass transfer kinetics study were received. Two extraction systems were investigated, №1: 6M $NaNO_3$ – $Nd(NO_3)_3$ – $Pr(NO_3)_3$ – three-n-butylphosphate (TBP) – kerosene and №2: $[Nd(NO_3)_3 \cdot 3TBP]$ – $[Pr(NO_3)_3 \cdot 3TBP]$ – kerosene – 0.1M HNO_3.

Received data was set in the developed mathematical model of extraction kinetics. Calculated kinetics curves match well with experimental ones.

The series of experiments with extraction of REE under conditions of periodical thermal oscillations with low mass transfer in both extraction systems were worked out. The influence of periodical oscillations of the temperature on extraction and stripping processes in the extraction systems is studied. Mathematical model of the non-stationary membrane extraction is enhanced including the dependence of extraction rate constants on temperature. The values of activation energy for direct and reverse reactions of extraction and

stripping reactions of Pr and Nd were calculated from experimental temporal dependencies of metal concentration and temperature by solving reverse kinetics problem using proposed mathematical model.

On the basis of the extraction rate constants and activation energies the optimization of the extraction process of separation of rare earth elements by liquid membrane under the influence of periodical oscillation of the temperature is carried out. The optimal conditions of separation by liquid membrane were found: frequency and amplitude of thermal oscillations, effective boundary area and liquid membrane flow rate.

The series of experiments with influence of periodical oscillations of the temperature on the extraction system using bulk liquid membrane between two extractors were carried out. The following extraction system was investigated: 6M $NaNO_3$ – $Nd(NO_3)_3$ – $Pr(NO_3)_3$ – TBP – kerosene – 0.1M HNO_3 with 0.5M TBP in kerosene as bulk liquid membrane. The mathematical model describes experimental data adequately.

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Materials of the Conferences

SORPTION OF GOLD IONS BY MODIFIED SHUNGITE

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Sorption procedures utilizing expensive anion-exchanger AM-2B have been widely applying in gold mining enterprises of Kazakhstan and CIS countries. There is a problem for utilization of new cheap sorbents at growing gold extraction. As results of the investigation a series of such anion-exchangers based a modified epoxy- and amino-containing schungites accessible in our region have been prepared [1-3]. The study carried out for recovery of silver and platinum ions by amined natural sorbents showed that surface-modified schungites recover noble metals ions for short duration time [2, 3].

The aim of the research is to study properties of amined schungite in relation to gold ions from model solution and their determination.

Schungite concentrate containing 80 % carbon was prepared by demineralization of the natural schungite (20 % carbon) with following granulation [4]. Amined schungite was obtained by polymerization of 2-methyl-5-vinylpyridine in sorbent granules, where nitrogen content by elemental analysis and polymer weight gain constituted 27.16 % and 2.51 %, respectively. Gold ions sorption was carried out under static conditions. A degree of gold ions recovery was determined as difference between the initial concentration of metal ions and residual one after sorption.

Study of sorption characteristics of the new sorbent based on amined schungite and containing polyvinylpyridineshowed that the presence of functional groups with donor nitrogen atomleads to its ability to recover noble metals ions.

In order to study optimal conditions for gold ions recovery utilizing amined schungite the kinetics of the process at ambient temperature was investigated. Dependence of a degree of recovery of gold ions by both the initial and modified schungite versus process duration showed that nature of surfacial groups of the samples causes discrepances in their kinetic characteristics. Equilibrium of metal ion distribution between the sorbent and solution under such conditions achieved within 4 hours with 80 % of gold ions for schungite, however the amined sample reached these results within 2 hours.

High kinetic characterisics of the last sample is mainly due to the presence of chemically active groeps and selectivity in relation to noble metal ions. It should be noticed that half saturation time for the natural sorbent is about 2 hours, and 15 minutes for the modified sample. It was found out that high degree of gold ions recovery (99.3 %) from chloride solutions at concentration 10 mg/l achieved using the amined schungite. Thus its sorption activity could emphasize its profitable for extraction of metal ions microadmixtures.

Acidity could effect on ratio of different forms of gold complex ions in solution. As it is known [5], ions exist as following anions: $AuCl_4^-$, $AuCl_3OH^-$, $AuCl_2OH_2^-$ etc. in chloride solutions. They could interact with functional groups of sorbent. Hydrolysis of Au(III) occurs at pH>3 and content of Au(III) hydrooxy chloride complexes decrease, as well as sorption of gold ions decreases. Therefore, sorption behavior was studied at pH within 1 to 3. It was found out that pH from 0.5 to 2 is an optimal acidity of solution. Analysis gold ions recovery degree onto amined schungite and HCl concentration let's talk about extraction completeness and its high efficiency.

Investigation of sorption activity of gold ions in dependence of pH of solution shows that they extracted in solid phase as a result of complex-formation of functional groups (ketonic, pyridine) and acidity of media characterizing a degree of ionization doesn't influence on the process. These results testify to the fact that in this case nitrogen atom of hetero-cycle participates in the sorption.

This fact makes ion-exchange mechanism be unlikely. Incidentally recovery of metal ions occurs due to complex-formation with electron-donor groups of pyridine as macromolecular

ligand. Therefore, gold ions are recovered predominantly on the investigated modified sorbent due to coordination of pyridine ring by nitrogen atom and by surface active sites of the natural sorbent. A study of possibility of regeneration of aminated schungite with the aim of its multiple application has been showed that sorbed gold ions can be desorbed by hydrochloric acid solution of thiocarbamide. It has been established that Au (III) is desorbed quantitatively by 7 % solution of thiocarbamide in 1M solution of HCl by 90 % at the room temperature. An increase of volume of eluent 2-3 times up results in a complete desorption of gold ions by 96-100 %.

Pyridine nitrogen forms complex compounds and displays selectivity in relation to transient elements. Hence kinetics of the process in the presence of cooper, cobalt and nickel ions (concentration of each metal constitutes 10 mg/l) has been studied to determine a possibility of recovery of gold ions on the aminated schungite. Analysis of sorption curves shows that selectivity of the investigated sorbent alters in the range Au>Cu>Co>Ni. In this case we have succeeded in extracting completely Au(III). A degree of recovery of cooper, cobalt and nickel ions constitutes 87, 56, 38 %, respectively. A saturation of the sorbent by metals ions occurs for 4-5 hours.

It was shown [1] that gold ions can be extracted quantitatively from transient elements from 0.5 M HCl solutions. Under established conditions a difference in the degree and the rate of their sorption on the investigated sorbent allows one to determine Au(III) in the presence of 10- and 50-fold quantities of Cu^{2+}, Co^{2+}, Ni^{2+} (Table). A selectivity of the investigated sorbent in relation to noble metal ions is due to the presence of symmetry-like π-orbitals in both the metal and pyridine ring that permit to suppose a formation of additional π-bond. This fact effects positively on the recovery and allows one to remove a main mass of accompanying elements and to recover gold ions in the presence of the admixture metals.

Thus it has been established on the basis of conducted investigations that schungite concentrate containing polyvinylpyridine in the granules is an effective sorbent of gold ions from hydrochloric acid solutions. Its high selectivity allows one to solve a task of concentration and extraction of gold ions even upon an excess of admixture elements.

Table. Sorption of gold ions by aminated schungite in the presence of accompanying metals (C_{Au}=10 mg/l, $m_{sorbent}$=0.5 g, V_{el}=50 ml, 0.5 M HCl)

Element (E)	Relation E:Au	R(Au), %
Cu (II)	10	98.9 ± 1.1
	50	98.8 ± 1.2
Co (II)	10	98.9 ±1.3
	50	98.9 ± 1.2
Ni (II)	10	98.9 ± 1.4
	50	98.9 ± 1.2

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