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SODIUM ASCORBATE INDUCES APOPTOSIS IN NEUROBLASTOMA CELL LINES BY INTERFERING WITH IRON UPTAKE

Carosio¹ R., Zuccari² G., Orienti² I., Mangraviti³ S., Montaldo¹ P.G.

¹Laboratory of Oncology, G. Gaslini Institute, Genova, Italy,

²Department of Pharmaceutical Sciences, University of Bologna, Bologna, Italy,

³Clinical Pathology Laboratory, G. Gaslini Institute, Genova, Italy

Neuroblastoma (NB) is an extra-cranial solid tumour of childhood. In spite of the good clinical response to first-line therapy, complete eradication of NB cells is rarely achieved. Thus, new therapeutic strategies are needed to eradicate surviving NB cells and prevent relapse. Sodium ascorbate has been recently reported to induce apoptosis of B16 melanoma cells through down-regulation of the transferrin receptor, CD71. Since NB and melanoma share the same embryologic neuroectodermal origin, we used different human NB cell lines to assess whether the same findings occurred.

We could observe dose- and time-dependent induction of apoptosis in all NB cell lines. Sodium ascorbate decreased the expression of CD71 and caused cell death within 24 h. An increase in the global and specific caspase activity took place, as well as an early loss of the mitochondrial transmembrane potential. Moreover, intracellular iron was significantly decreased after exposure to sodium ascorbate. Apoptotic markers were reverted when the cells were pretreated with the iron donor ferric ammonium citrate (FAC), further confirming that iron depletion is responsible for the ascorbate-induced cell death in NB cells.

Sodium ascorbate is highly toxic to neuroblastoma cell lines and the specific mechanism of vitamin C-induced apoptosis is due to a perturbation of intracellular iron levels ensuing TfR-downregulation.

Background

Neuroblastoma is the most common solid extracranial tumor of childhood [1]. This tumor has long fascinated clinicians and biologists due to its enigmatic behaviour. Extreme clinical heterogeneity is seen, including spontaneous regression. Still, a large part of neuroblastoma patients have highly aggressive disease that is refractory to intensive therapies and ultimately fatal. Current therapy for high risk neuroblastoma has reached a near-maximally tolerable state that includes cytoreductive and myeloablative therapies, radiation, autologous or allogenic bone marrow transplant, retinoids and immunomodulators, among others [2].

Therefore, less toxic and more effective therapy are to be found.

It has been recently reported that vitamin C is effective in a large panel of tumor cell lines [3,4]. Sodium Ascorbate (vitamin C) has a controversial history in cancer treatment. The discrepancy obtained in research and analysis by many authors was principally due to the different dose and route of administration of vitamin C and consequently to its plasma concentration [5-7].

Given this situation, the role of vitamin C in cancer treatment has been reexamined; in fact apparent responses of malignant dis-

ease to intravenous ascorbate therapy have appeared as case reports [5,6,8]. Some *in vitro* studies showed that ascorbate causes toxicity to cancer cells at concentration that do not affect normal cells [3,9,10]; furthermore, it was reported that melanoma cells were more susceptible to ascorbate toxicity than any other tumor cells. Ascorbate seems to induce apoptosis by inducing disequilibrium of iron uptake due to down-regulation of transferrin receptor [4]. Since melanoma and neuroblastoma have the same embryological neuroectodermal origin, we investigated whether neuroblastoma cell lines have the same susceptibility to vitamin C. First we studied the expression of transferrin receptor in neuroblastoma cell lines. Neoplastic cells were reported to express high rate of transferrin receptor, because growing cells have an increased requirement of iron [11]. Neuroblastoma cells are not an exception to this general rule, to the point that iron chelators have been proposed for the treatment of this kind of tumor [12,13].

Results

Effect of Sodium Ascorbate on neuroblastoma cell lines

We first investigated whether sodium ascorbate had cyto-toxic effects on neuroblastoma cell lines. Therefore we used sodium

ascorbate at millimolar concentration ranging from 0.5 mM to 3 mM for 24 hours. Vitamin C concentrations causing a 50% decrease in cell survival after 24 hours (EC_{50} values, table 1) were less than 2 mM for all five cell lines, as assessed by trypan blue exclusion method. Morphological inspection of treated cells, suggested that cell death took place through apoptosis rather than necrosis. This was confirmed by cytofluorimetric analysis of DNA content. There was a dose- and time-dependent increase of cells in the sub- G_1 phase of the cell cycle (typical of apoptotic cells) upon treatment with sodium ascorbate (fig. 1).

Table 1. EC_{50} values of vitamin C in human neuroblastoma cell lines. Cells were treated with sodium ascorbate for 24 h, EC_{50} values were determined by using trypan blue exclusion method. Values indicated are the mean \pm S.D. of three separate experiments.

Neuroblastoma cell lines	EC_{50} (mM) 24 h
HTLA-230	1.78 \pm 0.3
IMR-32	0.89 \pm 0.04
LAN-5	0.88 \pm 0.03
GI-LI-N	0.98 \pm 0.04
SH-SY5Y	1.44 \pm 0.2

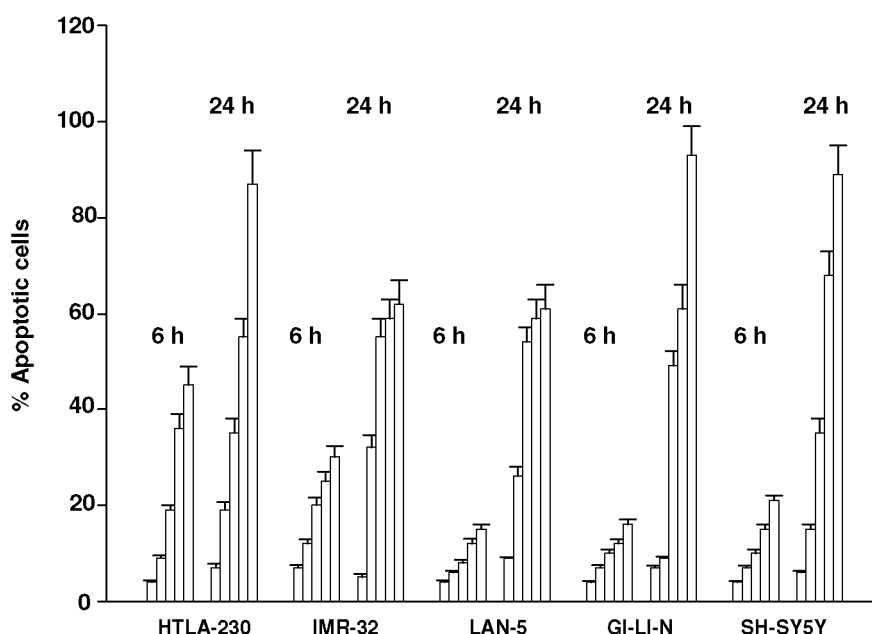


Figure 1. Sodium ascorbate induces apoptosis in neuroblastoma cell lines. Cells were seeded in six well plates and treated for 6 or 24 hours with increasing concentrations of sodium ascorbate. For each bar group, the concentration was: 0 mM (control), 0.5 mM, 1 mM, 2 mM, 3 mM. Cells were then processed and stained with propidium iodide as described in "Materials and Methods". The percent of cells in the sub- G_1 phase of the cell cycle were considered apoptotic. The data are the mean \pm S.D. from three independent experiments.

Sodium ascorbate induced-down regulation of TfR expression

Many tumor cells display high level of transferrin receptor to meet the increase in iron supply required by growing cells [11] and several authors have reported that antibodies against TfR have antiproliferative effects in vitro and in vivo [14,15]; furthermore, it was reported that in melanoma cells ascorbate induced down-regulation of cell

surface TfR [4]. In the present work, all the neuroblastoma cells analyzed expressed TfR (fig. 2). Addition of sodium ascorbate resulted in a concentration dependent down-regulation of TfR; besides, TfR change of expression seemed to be time independent, since there was a substantial decrease of CD71 expression at 6 hours and did not significantly decrease at 24 hours (fig. 2).

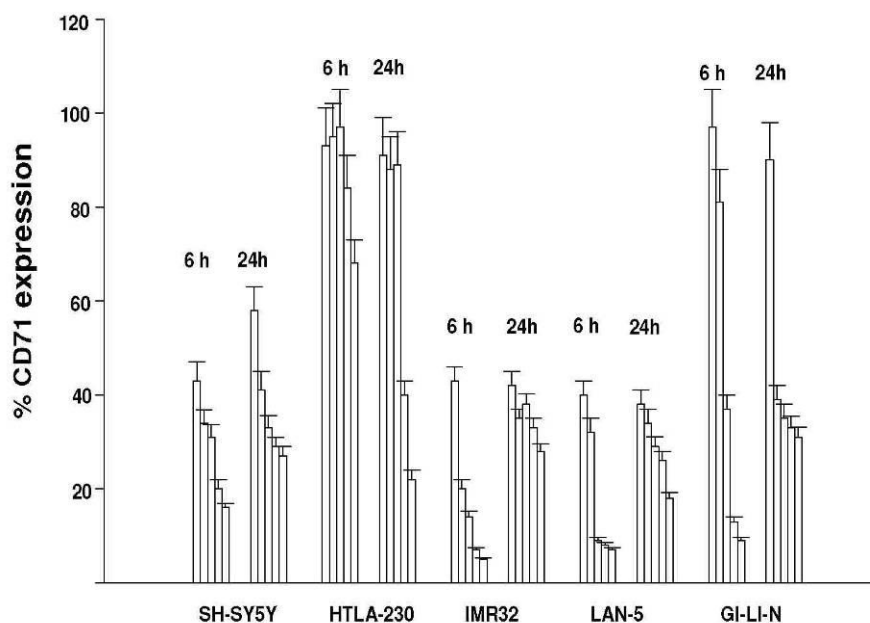


Figure 2. Membrane expression of TfR (CD71) by neuroblastoma cell lines and its modulation by sodium ascorbate. Cells were seeded in six well plates and treated for 6 and 24 hours with increasing concentrations of sodium ascorbate. For each bar group, the concentration was: 0 (control), 0.5 mM, 1 mM, 2 mM and 3 mM. Cells were then washed and incubated with a FITC-conjugated mouse monoclonal antibody specific to human CD71 and analyzed by flow cytometry. The data are the mean \pm S.D. from three independent experiments, each in triplicate.

Intracellular iron level

In order to find the possible mechanism of neuroblastoma cells apoptosis induced by vitamin C, we investigated whether this phenomenon was correlated with change in the intracellular iron levels; therefore we treated HTLA-230 and SH-SY5Y for 24 hours with 1.5, and 2 mM sodium ascorbate and iron level was then measured. As shown in fig. 3 vitamin C significantly reduced intracellular iron levels in a dose-dependent manner.

Effect of vitamin C on mitochondrial membrane potential

It is well established that the reduction of $\Delta\Psi_m$ also plays a key role in triggering apoptosis [16]. Treatment with vitamin C induced depolarization of the mitochondrial transmembrane potential in all neuroblastoma cell lines investigated (fig. 4, panel A2, A4, panel B2, B4).

To confirm that iron is involved in the induction of apoptosis we tested whether the iron donor ferric ammonium citrate (FAC) was able to prevent the sodium ascorbate-

induced apoptosis. To this aim before incubation with 2 mM of vitamin C, we treated HTLA-230 cells with 70 mg/ml of FAC for 3 hours; afterwards we assessed the induction of apoptosis by phosphatidylserine externalization using FITC-Annexin V binding.

The data depicted in fig. 5 show that the peak of apoptosis induced by ascorbate is nearly abolished by the pretreatment with the donor of iron FAC; in fact the percentage of Annexin V-positive cells decreased from 82% (cells incubated only with ascorbate) to 15% (cells incubated with ascorbate and pretreated with FAC). Similar results were obtained when we analyzed changes in the mitochondrial membrane potential ($\Delta\Psi_m$) in HTLA-230 and SH-SY-5Y, measured as the ratio of red-to-green JC-1 fluorescence (fig. 4). Treatment with vitamin C induced depolarization of the mitochondrial transmembrane potential in all neuroblastoma cell lines investigated and the effect was inhibited by FAC.

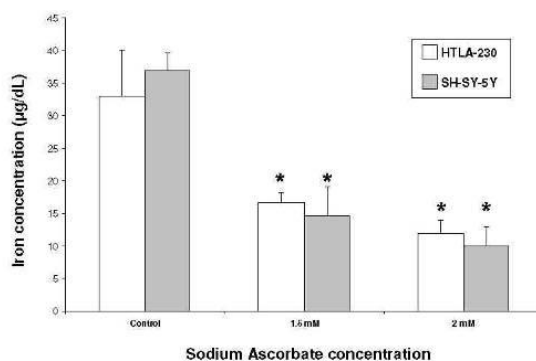


Figure 3. Reduction of intracellular iron levels by sodium ascorbate. 30×10^6 of either HTLA-230 or SH-SY5Y were treated with the indicated doses of sodium ascorbate for 24 hours and iron levels were measured in cell lysates. After terminating the incubation, cells were collected by scraping and washed three times with PBS and then lysed in specific buffer. Iron levels were analyzed with a Cobas Integra 800 system as described under "Material and Method". Values indicated are the mean \pm S.D. of three separate experiments.

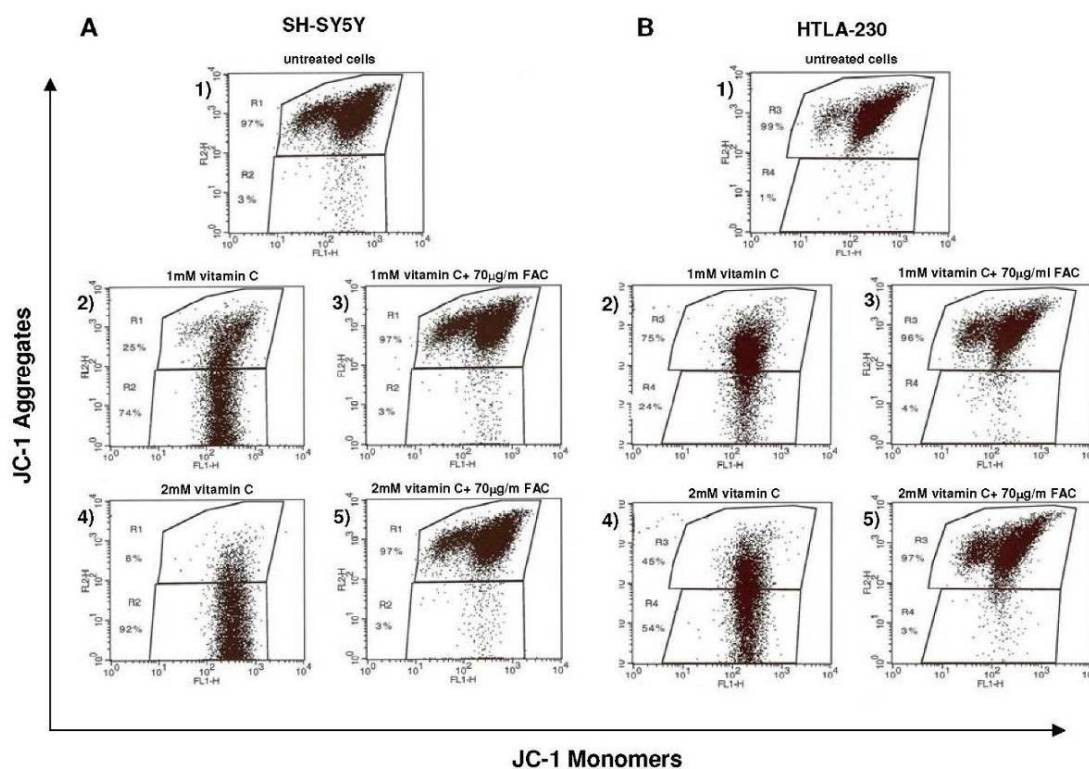


Figure 4. Representative example of cytofluorimetric analysis showing the effect of vitamin C alone or in combination with FAC, on the mitochondrial membrane potential of SH-SY5Y (panel A) and HTLA-230 (panel B) stained with JC-1 probe. In abscissa FL-1 (green fluorescence); in ordinate FL-2 (red fluorescence). Numbers represent the percentage of non-apoptotic red fluorescent cells (R1, R3) and that of apoptotic green fluorescent cells (R2, R4). Sodium ascorbate induces a marked increase in apoptosis which is fully prevented by treatment with FAC. SH-SY5Y and HTLA-230 were incubate in complete medium in the absence (A1, B1) or in presence of 1 mM sodium ascorbate (A2, B2) and 2 mM sodium ascorbate (A4, B4) for 16 hours. Cells were pre-treated (A3, A5, B3, B5) with 70 μ g/ml of FAC for 3 hours. Comparable results were obtained in three independent experiments.

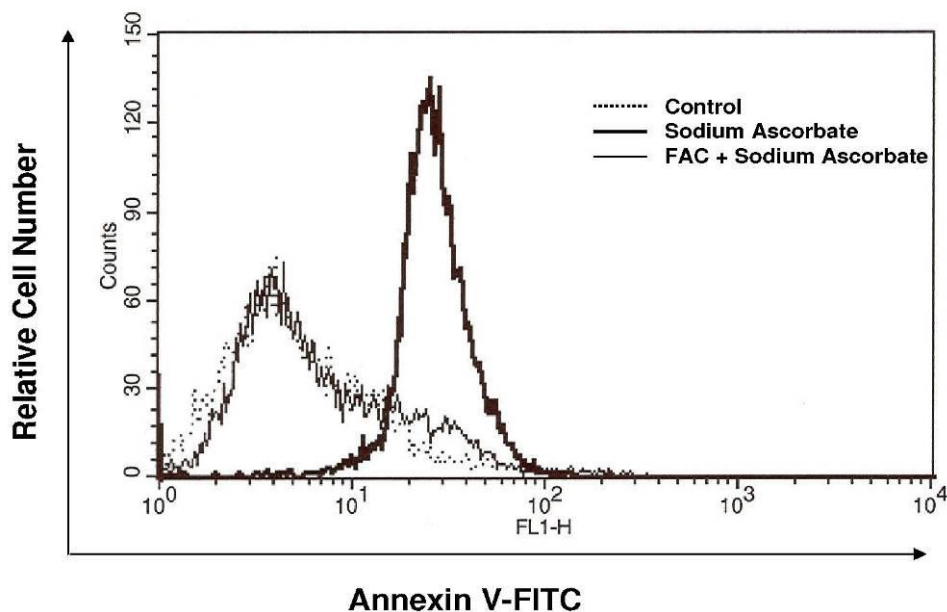


Figure 5. Effect of FAC on sodium ascorbate-induced apoptosis. HTLA-230 were grown in either complete medium alone (control cells), or medium containing 2 mM of sodium ascorbate (in the presence or absence of FAC 70 $\mu\text{g/ml}$). After 16 hours, cells detached in the medium were collected by centrifugation, resuspended and incubated with AnnexinV-FITC. Apoptosis was quantified as increased green fluorescence by flow cytometry. The data are the mean \pm S.D. from four independent experiments. Statistical analysis was done by Student's test (*, $p < 0.005$).

Sodium Ascorbate-induced apoptosis is mediated by caspases activation

Apoptosis arises from proteolytic activation of the cysteine proteases called caspases [17,18]. To verify the involvement of caspases in sodium ascorbate-induced apoptosis in neuroblastoma cell lines, we used a fluorescence-based pan-caspase activity assay kit. Cells were treated with increasing concentrations of sodium ascorbate for 12 and 24 hours before incubation with the fluorescent probe. The results showed a dose-dependent shift in fluorescence in all tested cell lines, revealing a significant participation of caspases in ascorbate-induced apoptosis (in fig. 6 are represented only SH-SY5Y and HTLA-230, similar data were obtained for GI-LI-N, IMR-32 and LAN-5, data not shown). Moreover the activation of caspases

was an early event; in fact there was not significant difference in fluorescence increase between 12 and 24 hours of incubation. To understand which caspases was mainly involved in the apoptotic mechanism, we used all the commercially available kits for single caspases (i.e., caspase-1, caspase-2, caspase-3&7, caspase-6, caspase-8, caspase-9, and caspase-10) and measured the increase in fluorescence after 16 hours in SH-SY5Y and HTLA-230 cell lines. As depicted in fig. 7, all the above caspases showed a similar pattern of activation, in particular in SH-SY5Y caspases were already activated at 1 mM ascorbate. Although these experiments did not allow us to individuate a hierarchy of activation, they clearly confirmed the apoptotic nature of cell death induced by sodium ascorbate in neuroblastoma cell lines.

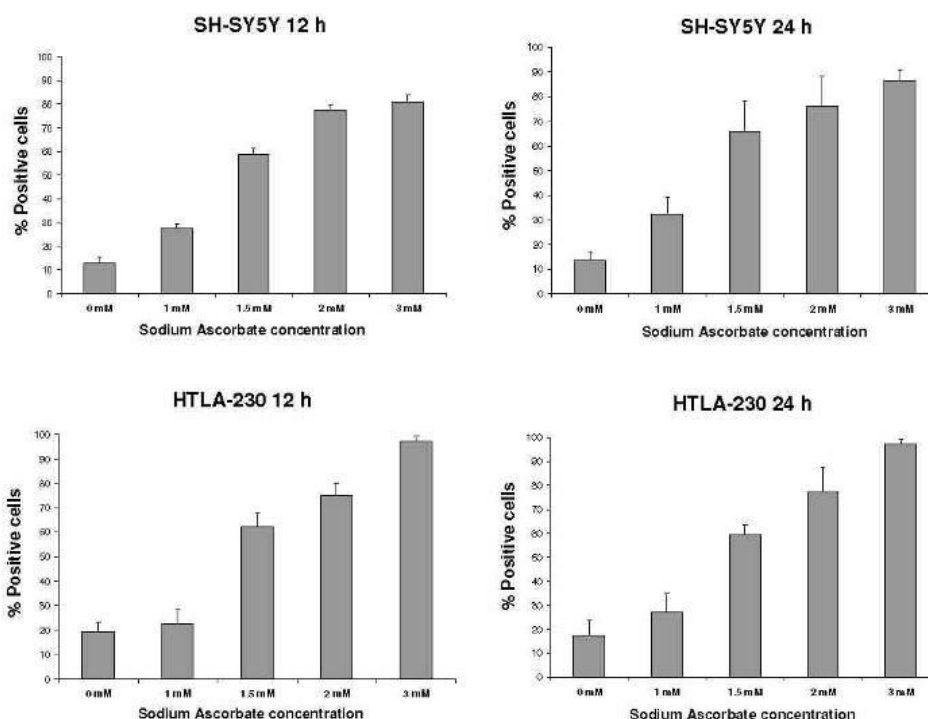


Figure 6. Effect of vitamin C on caspases activation. HTLA-230 and SH-SY5Y were treated with the indicated concentrations for 12 and 24 hours. After detachment, cells were stained with the pan-caspase-fluorescent-probe z-VAD-FMK according to the manufactures instructions. Relative increases in fluorescence emission were detected by single color flow cytometry. The data are the mean \pm S.D. from three independent experiments.

Discussion

The effect of vitamin C on cancer has been a subject of great controversy, and vast literature exists on this topic. Thirty years ago Cameron, Campbell and Pauling reported that high-dose vitamin C had beneficial effect for patient with terminal cancer. Subsequently, double-blind, randomized clinical trials, conducted by Moertel of the Mayo clinic, failed to show any benefit and the use of sodium ascorbate in cancer treatment was abandoned [19-24]. However, Moertel's results were not comparable to those of Cameron, as ascorbate was given orally and not intravenously. It was not recognized that the route of administration might produce large difference in plasma concentration. Recent clinical data show that when given i.v., ascorbate plasma concentration is 25 fold higher respect that of the same oral dose [7].

Sodium ascorbate produces cytotoxic effect in an array of malignant cell lines, in-

cluding melanoma cells which are particularly susceptible [3,4,9,10].

In light of these results we investigated the effect of sodium ascorbate against neuroblastoma.

Our data show that sodium ascorbate killed neuroblastoma cells, using lower concentrations compared to those active in other tumor cell lines; in fact vitamin C, in the range of 0.5 to 3 mM turned out to be strongly cytotoxic. To broadly cover the phenotype of the tumor we used five neuroblastoma cell line including MYCN amplified (HTLA-230 and IMR-32) and not-MYCN amplified (SH-SY5Y). Sodium ascorbate-induced cell death was apopto-sis, as documented by our experiments regarding the decrease of mitochondrial membrane potential, the phosphatidylserine externalization, the increase of cells in the sub-G₁ phase of the cell cycle and caspases activation.

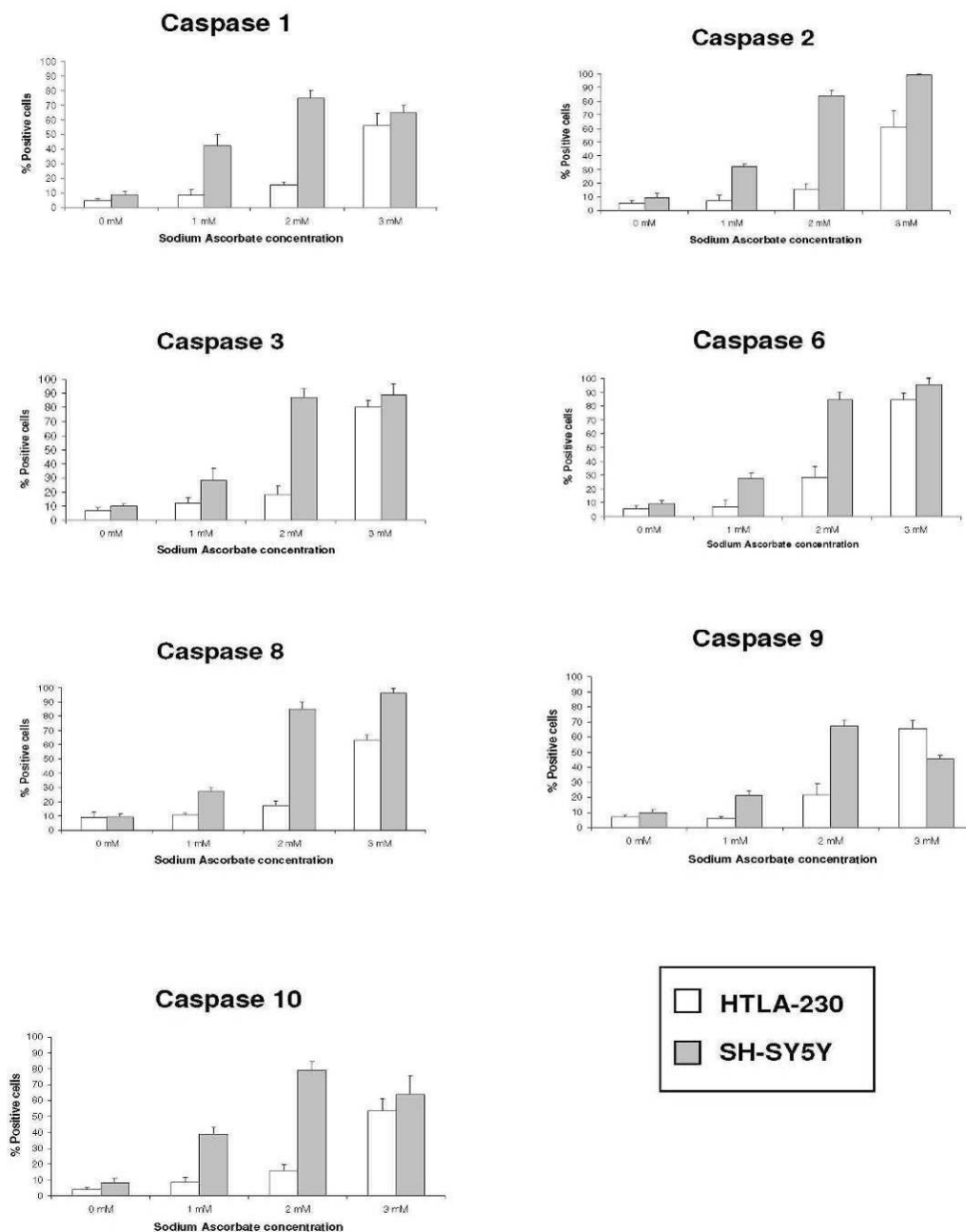


Figure 7. Effect of sodium ascorbate on single caspases activation. HTLA-230 and SH-SY5Y were incubated in the absence (0 mM) or presence of the indicated concentrations for 16 hours and then analyzed for single caspases by flow cytometry as described in Material and Method. Coloums, mean of three different experiments, each done in triplicate; bars, SD.

In this study we show that all the caspases are activated by the incubation with vitamin C, in fact, not only caspases related to the mitochondrial pathway were found to be activated but also those related to the death receptor pathway. The two pathways, extrinsic and intrinsic, are probably interconnected by caspase-8 mediated cleavage of the pro-

apoptotic Bcl-2 family member Bid, producing a truncated Bid (tBid) fragment that promotes the mitochondrial release of proteins from the intermembrane space. In particular, it is known, that the release of cytochrome c induces the activation of caspase proteases through the induction of apoptosome formation [25].

To clarify if ascorbate-mediated cytotoxicity was due to perturbation in the iron uptake, we measured intracellular iron level of HTLA-230 and SH-SY5Y after 24 hours of incubation with increasing doses of vitamin C. We could observe a dose-dependent decrease of iron levels; furthermore, pretreatment of cells with the iron donor FAC completely prevented sodium ascorbate-induced apoptosis. Thus, the percentage of Annexin V positive cells decreased to that of untreated cells and, in a similar way, the pretreatment with FAC completely abolished the ascorbate-induced reduction of mitochondrial membrane potential.

Several studies report the correlation of iron level with apoptosis [26,27]. Virtually all living cells have an absolute requirement for iron, since many Fe-containing proteins catalyze key reactions involved in energy metabolism (cytochromes, mitochondrial aconitase, Fe-S proteins of the electron transport chain), respiration (hemoglobin), and DNA synthesis (ribonucleotide reductase) [11]. Inhibition of ribonucleotide reductase has been proposed as the cause of the growth arrest that occurs in cell deprived of iron because this enzyme requires iron to reduce ribonucleotides to form the substrate of DNA synthesis [28-30]. The regulated uptake and availability of iron is closely linked to cellular proliferation. Three proteins, the iron-transport transferrin, the transferrin receptor on the cell surface and ferritin are essential for making iron available for cellular use. Many neuroblastomas produce very large amount of ferritin [12]. In addition to being incorporated into heme proteins and enzymes, iron may participate more directly in the regulation of cell growth and apoptosis of neuroblastoma; in fact neuroblastoma cells appear to be unusually sensitive to the cytotoxic and cytostatic effect of iron chelators [31]. Furthermore the mechanism by which vitamin C decreased intracellular iron level seems to be correlated with the down-regulation of transferrin receptor. Our data are consistent with the fact that tumor cells express high level of transferrin receptor to

meet the increase in iron required by growing tumor tissue [11].

Some *in vitro* studies showed that ascorbate causes toxicity to cancer cells at concentrations that do not affect normal cells [3,9]; this phenomenon is probably due to a tumor specific intracellular transport of ascorbate. Extracellular ascorbate is oxidized, transported as dehydroascorbic acid, and reduced intracellularly to ascorbate [32]. Many cell types transport ascorbate only in its oxidized form, through facilitated glucose transporters [33]. Tumor cells have an increased requirement for glucose [34] and to compensate for this they increase the expression of glucose transporters. This allows ascorbate to act as a selective, non toxic to normal cells, chemotherapeutic.

Conclusion

This study demonstrates that sodium ascorbate is highly toxic to neuroblastoma cell lines and the specific mechanism of vitamin C -induced apoptosis is due to a perturbation of intracellular iron levels ensuing TfR-downregulation.

This work, together with others, supports the use of vitamin C as an anticancer agent; in particular we suggest exploring the use of high dose intravenous ascorbate in controlled studies. Besides, vitamin C is relatively tumor specific, non toxic and inexpensive, in contrast to many chemotherapeutic agents in use.

Methods Reagents

Sodium ascorbate and ferric ammonium citrate (FAC) were purchased from Sigma (St. Louis, MO). Ascorbate was dissolved in PBS, pH 7.4, and prepared immediately before use.

Monoclonal antibody to transferrin receptor (TfR, CD71) was obtained from BD biosciences (San Jose, CA).

Cells

To broadly cover the phenotypes exhibited by NB cell *in vitro*, we used five human NB cell lines: SH-SY5Y [35], HTLA-230 [36], LAN-5 [37], IMR32 [38] and GI-LI-N [39]. All cell lines were grown in Dulbecco's modified Eagle medium supplemented with

10% fetal bovine serum (GIBCO Milan Italy) and 50 UI/ml penicillin, 50 µg/ml streptomycin and 2 mM L-glutamine (all reagent from Sigma). Cells were cultured at 37°C in a humidified atmosphere of 5% CO₂ in air. Most experiments were performed on SH-SY5Y and HTLA-230, unless otherwise specified.

Trypan blue exclusion method

The effects of sodium ascorbate on cell death were determined by trypan blue exclusion method as described elsewhere. Briefly, cells were seeded in 6-well plates, and, after 48 h, treated in absence or presence with various concentrations of vitamin C for 24 hours. Then, cells were trypsinized and diluted in growth medium. The cells were then counted under a phase-contrast microscopy, in a Burker counting chamber, in the presence of trypan blue (Sigma) solution at a 1:5 ratio, cells: trypan, (v/v).

Cell cycle analysis

HTLA-230, IMR-32, LAN-5 and GILI-N were seeded in six well plates and treated in the absence or presence of increasing concentration of sodium ascorbate (0.5 mM, 1 mM, 2 mM and 3 mM) for 6 or 24 hours. Cells were harvested and washed with cold PBS, centrifuged at 1200 rpm and stored overnight in ethanol at -20°C. The following day, cells were washed with cold PBS, resuspended in 0.1% NP40, 100 µg/ml RNase A, 35 µg/ml propidium iodide (PI) and incubated for 20 minutes at 37°C. The stained cells were analyzed for DNA content by flow cytometry in a FACScan (Becton Dickinson, San Jose, CA) equipped with a 15-mW argon ion laser at 448 nm.

Measurement of intracellular iron levels

HTLA-230 cells (30×10^6) were cultured for 24 hours in presence or absence of 1.5 or 2 mM sodium ascorbate. Cells were then washed with PBS and homogenized in lysis buffer (10 mmol/L Tris-HCl, 144 mmol/L NaCl, 0.5% NP-40, 0.5% SDS, 1 mmol/L Na₃VO₄ plus protease inhibitors). Iron concentration in cell lysates was performed with a Cobas Integra 800 system (Roche Diagnostics GmbH, Mannheim, Germany) as routinely assessed on plasma

or serum samples by an Iron Test (Roche Diagnostics); iron concentration was estimated by absorbance at 552 nm.

Measurement of mitochondrial membrane potential

Mitochondrial membrane potential was detected with the MitoPT™ Mitochondrial Permeability Transition Kit (Alexis).

Loss of the mitochondrial permeability transient event (PT) provides an early indication of the initiation of cellular apoptosis. This process is typically defined as a collapse in the electrochemical gradient across the mitochondrial membrane, as measured by the change in the membrane potential ($\Delta\psi_m$). Loss of the mitochondrial Δ^*P , can be detected by a unique fluorescent cationic dye, 5, 5', 6, 6'-tetrachloro-1, 1', 3, 3'-tetraethylbenzamidozolocarbocyanine iodide, commonly known as JC-1, incorporated into the MitoPT™ kit. The dye penetrates cells and healthy mitochondria. Once inside a healthy non-apoptotic cell, the reagent bearing a positive charge, enters the negatively charged mitochondria where it aggregates and fluoresces red. When the mitochondrial Δ^*P collapses in apoptotic cells, the reagent no longer accumulates inside the mitochondria. Instead, it is distributed throughout the cell. When dispersed in this manner, the MitoPT™ reagent assumes a monomeric form, which fluoresces green. Then, it is easily distinguishable between non-apoptotic red fluorescent and apoptotic green fluorescent cells [40,41].

HTLA-230 and SH-SY5Y cells (1×10^6 cell/ml) were pre-treated, or not, for 3 hours with 70 ng/ml FAC and then treated with sodium ascorbate for 18 hours. Cells were washed and resuspended in 0.5 ml of $1 \times$ MitoPT and incubated at 37°C for 15 minutes. After incubation, cells underwent to multi-parameter analysis using a flow cytometer.

Annexin assay

Apoptotic cells were detected by Annexin V staining using the Annexin V-FITC kit purchased from Pharmingen (San Diego,

CA) following the instructions of the manufacturer.

Briefly, HTLA-230 treated with sodium ascorbate and with or without FAC were washed with cold PBS and then resuspended in $1 \times$ binding buffer at a concentration of 5×10^5 cell/ml.

195 μ l of cell suspension was transferred to a tube, then 5 μ l of Annexin V-FITC was added and cells were incubated at room temperature for 10 minutes in the dark with gentle vortexing. Cells were then washed and resuspended in 200 μ l of $1 \times$ binding buffer and analyzed by flow cytometry.

Caspase activity assay

The FLICA Apoptosis Detection Kit (Alexis, San Diego, CA) was used to detect ascorbate-induced activation of caspases in neuroblastoma cells, according to the manufacturer instructions, by flow cytometry. The FAM-VAD-FMK reagent provided in the kit is a carboxyfluorescein (FAM) derivative of benzyloxycarbonyl valyl alanyl aspartic acid fluoromethyl ketone (zVAD-FMK), which is a potent inhibitor of caspase activity. It enters the cell and irreversibly binds to activated caspases (caspases 1, 2, 3, 4, 5, 6, 7, 8, and 9) allowing for direct detection of pan-caspases activity by green fluorescence in live cells [42]. Briefly, cells were detached by trypsinization and centrifuged at $400 \times g$ for 5 minutes at room temperature. Cell supernatants were removed and the pellets resuspended in a buffer containing the pan-caspase-fluorescent probe. After 1 hour of incubation, samples were washed and analyzed by single color flow cytometry at 488 nm for fluorescein on the FL1 channel.

To assess which caspase was mainly involved in ascorbate-induced apoptosis, we used all the commercially available kits specific for single caspases, i.e., FAM-YVAD-FMK for caspase-1, FAM-VDVAD-FMK for caspase-2, FAM-DEVD-FMK for caspases-3&7, FAM-VEID-FMK for caspase 6, FAM-LETD-FMK for caspase 8, FAM-LEHD-FMK for cas-pase 9 and FAM-AEVD-FMK

for caspase-10. All kits were obtained from Alexis (San Diego, CA).

Competing interests

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

Authors' contributions

All the authors have contributed significantly to the work.

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FUNCTIONAL ANALYSIS OF CANCER-ASSOCIATED EGFR MUTANTS USING A CELLULAR ASSAY WITH YFP-TAGGED EGFR INTRACELLULAR DOMAIN

Gunst¹ M.M., Gallegos-Ruiz¹ M.I., Giaccone^{1,2} G., Rodriguez^{1,3} J.A.

¹*Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands,*

²*Medical Oncology Branch, CCR, National Cancer Institute, NIH, Bethesda, MD 20892-1906, USA,*

³*Department of Genetics, Physical Anthropology and Animal Physiology, University of the Basque Country, 48940 Leioa, Spain*

The presence of EGFR kinase domain mutations in a subset of NSCLC patients correlates with the response to treatment with the EGFR tyrosine kinase inhibitors gefitinib and erlotinib. Although most EGFR mutations detected are short deletions in exon 19 or the L858R point mutation in exon 21, more than 75 different EGFR kinase domain residues have been reported to be altered in NSCLC patients. The phenotypical consequences of different EGFR mutations may vary dramatically, but the majority of uncommon EGFR mutations have never been functionally evaluated.

We demonstrate that the relative kinase activity and erlotinib sensitivity of different EGFR mutants can be readily evaluated using transfection of an YFP-tagged fragment of the EGFR intracellular domain (YFP-EGFR-ICD), followed by immunofluorescence microscopy analysis. Using this assay, we show that the exon 20 insertions Ins770SVD and Ins774HV confer increased kinase activity, but no erlotinib sensitivity. We also show that, in contrast to the common L858R mutation, the uncommon exon 21 point mutations P848L and A859T appear to behave like functionally silent polymorphisms.

The ability to rapidly obtain functional information on EGFR variants of unknown relevance using the YFP-EGFR-ICD assay might prove important in the future for the management of NSCLC patients bearing uncommon EGFR mutations. In addition, our assay may be used to determine the response of resistant EGFR mutants to novel second-generation TKIs.

Approximately 80% of lung cancers, the most frequently diagnosed type of human tumor, are classified as non-small cell lung cancer (NSCLC). Novel therapeutic agents for the treatment of NSCLC patients are currently under intense experimental and clinical investigation, with the goal of increasing their antitumor effect while reducing general toxicity. These agents specifically target cellular pathways necessary for the survival of cancer cells. The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase (TK) whose activation initiates signal transduction through critical cellular pathways, such as those mediated by Akt and ERK, and thus plays an important role in controlling cell homeostasis [1]. EGFR is over-expressed or aberrantly activated in different types of human tumors, contributing to the malignant phenotype of cancer cells, and targeted inactivation of EGFR is being intensively explored as a cancer therapeutic approach [2]. As a result of these investigations, several small-molecule EGFR tyrosine-kinase inhibitors (TKIs), such as gefitinib and erlotinib,

have been developed and are currently available in the clinic. In large clinical studies of gefitinib and erlotinib, it became apparent that a minor subset of NSCLC patients is extremely sensitive to treatment with EGFR-TKIs [reviewed in [3]]. Subsequently, the analysis of EGFR gene sequence revealed the presence of somatic mutations in the kinase domain of the receptor in most responding patients [4-6]. The association between the presence of EGFR mutations and response to TKIs has been confirmed through the analysis of thousands of NSCLC tumor samples worldwide. These results raise the possibility that EGFR mutational analysis may be implemented for the management of NSCLC patients [7].

Approximately 80% of the EGFR mutations detected are short deletions in exon 19 affecting the amino acid sequence ELREA (Del746-750), or a point mutation in exon 21 resulting in the amino acid change L858R. However, the data accumulated in the past three years have uncovered the large allelic heterogeneity that characterizes EGFR kinase

mutations. Thus, a survey of the COSMIC mutation database [8] shows that more than 75 different EGFR kinase domain residues have been reported to be altered in NSCLC patients.

The functional characteristics of the two most common types of EGFR alterations, the exon 19 deletions and the L858R point mutation, have been studied in detail using biochemical assays, cell-based systems and mouse models [4-6], [9-14]. Additionally, a limited number of less common mutant alleles of EGFR have been tested using transfection-based approaches [15-22]. Nevertheless, the biological effect of most uncommon EGFR alterations has never been evaluated. The phenotypical effect of the particular alteration detected in tumor cells may largely account for the response of the patient to treatment. In this regard, certain mutations, such as the T790M amino acid change, have been shown to confer resistance to gefitinib and erlotinib [reviewed in [7]]. Second-generation TKIs, which bind covalently to EGFR and may be active against these resistant mutants, are currently being developed.

To allow for a more rapid characterization of untested EGFR mutants, and to facilitate the testing of novel potential anti-EGFR agents, we aimed here to establish a simple cellular assay to evaluate the effect of EGFR mutations and the response of different EGFR variants to erlotinib. To this end, we used site-directed mutagenesis to introduce cancer-associated mutations into an YFP-tagged fragment of EGFR intracellular domain (YFP-EGFR-ICD). These chimerical proteins were transiently expressed in human cells, and the effect of their expression was assessed on a single-cell basis using immunofluorescence with phosphorylation-specific antibodies.

We demonstrate here that the YFP-EGFR-ICD-based assay can be used to evaluate the relative kinase activity and erlotinib sensitivity of EGFR mutants, and we use this approach to test several uncommon EGFR mutations.

Results

Increased autophosphorylation of YFP-tagged EGFR intracellular domain the common EGFR Del746 mutation

We generated an YFP-tagged fragment of EGFR (Figure 1A) encompassing residues 688–1116 (the numbering system includes the 24 amino acid signal peptide of EGFR). This fragment, termed YFP-EGFR-ICD, contains the TK domain, as well as sequences from the adjacent regulatory motif, but lacks the extracellular and the juxtamembrane domains of the receptor. The Del746-750 mutation (hereafter called Del746) was next introduced into YFP-EGFR-ICD using site-directed mutagenesis. This mutant, representative of the common and well-characterized exon 19 deletions, was used as a positive control in the initial experiments to test the suitability of our system.

MCF-7 breast cancer cells were transfected with plasmids encoding YFP-EGFR-ICD wt or YFP-EGFR-ICD Del746, and examined using fluorescence microscopy. Approximately 30% of the cells expressing the mutant EGFR ICD showed long lamellipodial protrusions, which were not observed in cells expressing the wt fragment (Figure 1B). Cells were fixed 24 hours after transfection and immunostained using specific primary antibodies to detect phosphorylation of EGFR tyrosine residues Y869 and Y1092. Using secondary antibodies conjugated to the red fluorophore Alexa Fluor-594 (AF-594) and YFP positivity as a marker of transfection, we were able to examine YFP-EGFR-ICD phosphorylation in a single-cell basis (Figure 1C). Non-transfected MCF-7 cells did not contain detectable levels of phosphorylated EGFR. YFP-EGFR-ICD wt-transfected cells showed no or barely detectable pY869 or pY1092. In contrast, cells expressing comparable levels of the mutant protein (as indicated by the intensity of the YFP signal) showed a robust immunostaining signal for both residues. The anti-pY1092 antibody provided the clearest result, and was therefore used in subsequent analyses. Similar experiments were carried out with a shorter EGFR fragment containing only the TK domain (amino acids 688–982), but no autophosphorylation (pY869) was detected (data not shown).

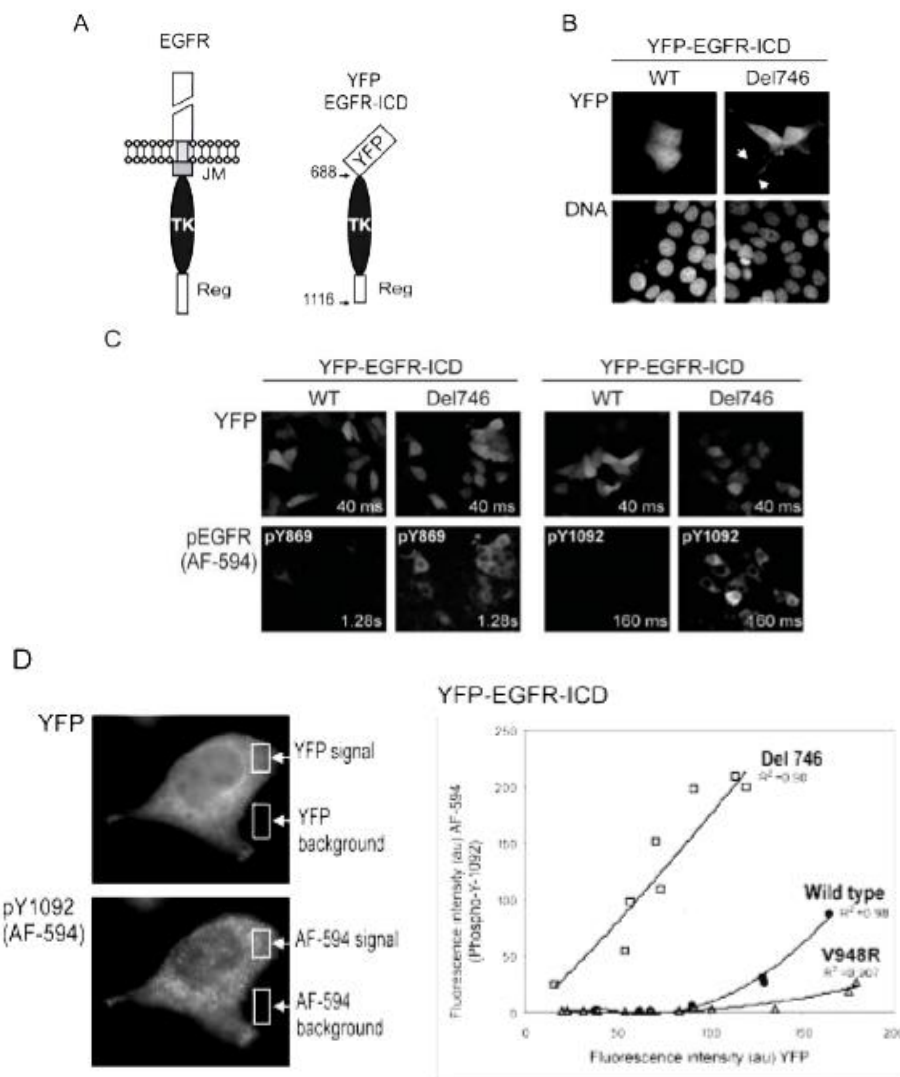


Figure 1. Common NSCLC-associated EGFR mutations lead to increased autophosphorylation of an YFP-tagged EGFR intracellular domain. *A*. Schematic representation of full-length EGFR and YFP-EGFR-ICD. The amino acid numbering includes the 24 residues of the signal peptide. YFP-EGFR-ICD contains the tyrosine kinase (TK) domain and part of the regulatory region (Reg), but lacks the extracellular and juxtamembrane (JM) domains. *B*. Expression of YFP-EGFR-ICD Del746 induces morphological changes in MCF-7 cells. Unlike cells transfected with wild type (WT) YFP-EGFR-ICD, MCF-7 cells expressing YFP-EGFR-ICD Del746 frequently show long lamellipodial protrusions (arrowheads). *C* Using immunofluorescence, increased autophosphorylation of YFP-EGFR-ICD Del746 at tyrosine residues Y869 (left set of panels) and Y1092 (right set of panels) can be detected. Phosphorylation is virtually undetectable in cells expressing YFP-EGFR-ICD WT. Images were taken using $160\times$ magnification and the exposure time indicated inside the panels. The fluorescent signal was consistently brighter using the anti-pY1092 antibody (note the shorter exposure time used). *D*. Semi-quantitative comparison of YFP-EGFR-ICD autophosphorylation level using computer-assisted image analysis. Images of several transfected cells ($400\times$ magnification) were taken using 40 ms (YFP) or 160 ms (AF-594) exposure times. The fluorescence intensity in the green and the red channels was measured within a cytoplasmic area (YFP signal and AF-594 signal), and within an area outside the cells (background). In the graph, the intensity of the YFP and AF-594 fluorophores for each cell was plotted against each other using Excel, and the best-fitting trend lines (highest R^2) were added. At similar expression levels (YFP intensity), the level of pY1092 is higher for YFP-EGFR-ICD bearing the Del746 mutation (white squares) than for the wild type protein (circles). The V948R mutation (open triangles) virtually abrogated autophosphorylation. The experiment was repeated twice with similar results. Graph shows the data from one experiment. au: arbitrary units.

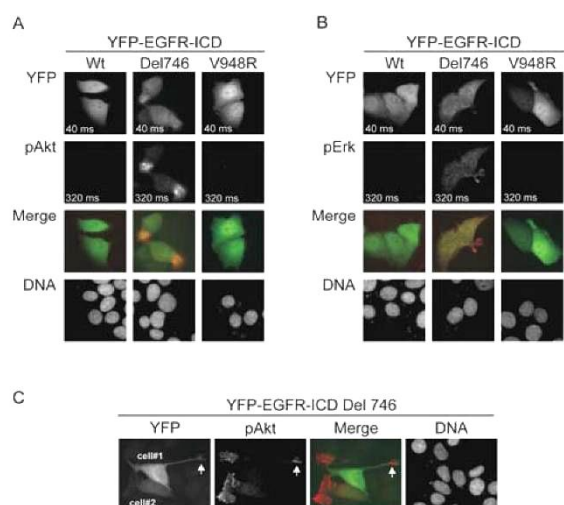


Figure 2. Activation of Akt and Erk pathways in cells expressing mutant YFP-EGFR-ICD Del746. A. Panels show representative images (400X) of MCF-7 cells expressing YFP-EGFR-ICD wild type, Del746 or V948R, analyzed by immunofluorescence to detect phosphorylated Akt (pAkt). Phosphorylation of endogenous Akt was only detected in cells expressing the Del746-bearing protein. B. A similar analysis was carried out to detect phosphorylated ERK (pERK). Only cells expressing YFP-EGFR-ICD Del746 contained detectable levels of endogenous pERK. Exposure time is indicated inside the panels. DNA was counterstained with Hoechst. C. Images (400X) illustrate two morphological characteristics of Akt phosphorylation in cells expressing YFP-EGFR-ICD Del746. On one hand, pAkt showed a preferential localization to membrane ruffles, and often accumulated at the tip of lamellipodial protrusions (arrowhead). On the other hand, cells expressing high (cell#1) or low (cell#2) levels of YFP-EGFR-ICD Del746, often contained similar levels of pAkt.

We used computer-assisted image analysis to measure the intensity of the YFP and AF-594 signals in the cytoplasm of several individual cells (Figure 1D, left images). In addition to wt and Del746, an YFP-EGFR-ICD protein bearing the experimental V948R mutation was tested. This amino acid change has been shown to maintain EGFR kinase domain in an inactive conformation [23]. In line with previous data, autophosphorylation was dramatically increased by the Del746 mutation (Figure 1D, graph). It should be pointed out that cells expressing very high levels of the wt ICD showed weak but de-

tectable Y1092 phosphorylation. The V948R change, as expected, virtually abrogated ICD autophosphorylation even at the highest levels of expression.

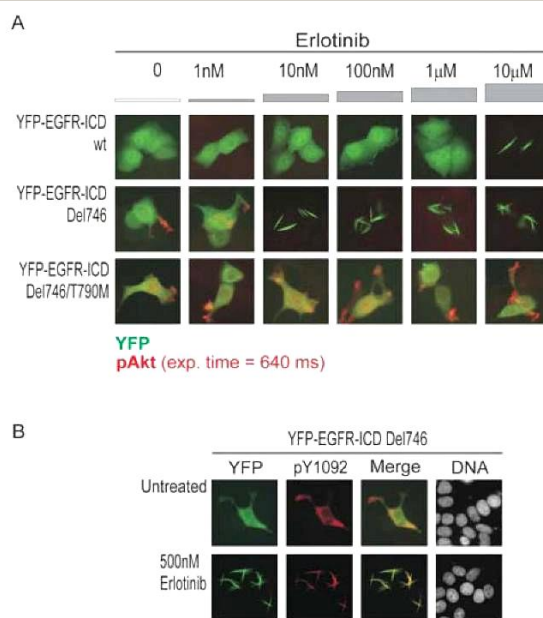


Figure 3. Evaluating erlotinib sensitivity of EGFR mutants in the context of YFP-EGFR-ICD. A. Representative examples of MCF-7 cells expressing YFP-EGFR-ICD wild type, Del746 or Del746/T790M (green), stained for endogenous phosphorylated Akt (red). Cells were treated for 20 hours with the indicated concentration of erlotinib. The different response of each EGFR variant to erlotinib treatment is readily visualized by immunofluorescence. YFP-EGFR-ICD wild type does not induce Akt phosphorylation, and relocates into thick cytoplasmic fibrils at 10 μ M erlotinib. One thousandfold lower concentration of the drug (10 nM) inhibited Del746-induced Akt phosphorylation, and caused fibrillar relocation of the ectopic protein. The double mutant Del746/T790M did not form fibrils and induced Akt phosphorylation even in the presence of 10 μ M erlotinib. B. Images show that YFP-EGFR-ICD Del746 (green) remains phosphorylated at Y1092 (red) after relocating into fibrils in the presence of erlotinib.

Altogether, these results demonstrate that the effect of NSCLC-related EGFR mutations on basal autophosphorylation can be rapidly evaluated on a single cell basis using transient transfection of YFP-EGFR-ICD and immunofluorescence.

Activation of EGFR downstream signaling pathways in cells expressing mutant YFP-EGFR-ICD Del746

Signal transduction downstream of EGFR and, ultimately, the cellular response to EGFR activation, relies on the integrated activity of several intracellular signaling pathways, such as those mediated by Akt or ERK. Phosphorylation of ERK and Akt at specific residues, which constitutes a key activating event in these pathways, is widely used as a marker of active EGFR downstream signaling.

MCF-7 cells transfected with YFP-EGFR-ICD wt, Del746 or V948R, were immunostained using specific antibodies to detect endogenous phosphorylated Akt (pAkt-S473) and phosphorylated ERK (pERK-T202/Y204). The levels of pAkt (Figure 2A) and pERK (Figure 2B) were undetectable in non transfected cells as well as in cells expressing YFP-EGFR-ICD wt or YFP-EGFR-ICD V948R. In contrast, phosphorylation of both Akt and ERK was clearly detected by immunofluorescence in YFP-EGFR-ICD Del746-transfected cells. A more intense signal was consistently obtained with the anti-pAkt antibody, which was therefore used in subsequent experiments. As illustrated in Figure 2C, phosphorylated Akt in YFP-EGFR-ICD Del746-transfected MCF-7 cells localized preferentially to membrane ruffles and the tip of the lamellipodial protrusions mentioned above. Remarkably, we did not observe a correlation between the expression levels of ectopic EGFR ICD and the intensity of the endogenous pAkt signal.

The sensitivity of EGFR mutants to erlotinib can be evaluated in the context of YFP-EGFR-ICD

We next evaluated the response of the Del746 mutant in the context of YFP-EGFR-ICD to the TKI inhibitor erlotinib. The TKI-resistant double mutant Del746/T790M [24,25] was also tested. Four hours post-transfection, erlotinib at a final concentration ranging from 1 nM to 10 μ M was added to the culture medium, and cells were incubated for 20 hours. Samples were then fixed and immunostained using the anti-pAkt antibody. As illustrated in Figure 3A, no effect of erlotinib on cells expressing YFP-EGFR-

ICD wt was noted up to 1 μ M. At 10 μ M, erlotinib induced the relocation of the chimeric protein to thick cytoplasmic filaments, reminiscent of actin cables [26]. EGFR can interact with actin [27], and the ICD fragment used in our assay includes the actin binding domain of EGFR. However, rhodamine-conjugated phalloidin failed to show colocalization with YFP-EGFR-ICD filaments (data not shown), suggesting that they do not contain actin. In cells expressing YFP-EGFR-ICD Del746, Akt phosphorylation was detected in both untreated samples and samples treated with 1 nM erlotinib. However 10 nM or higher concentration of the drug abrogated Akt phosphorylation and induced fibril formation. Surprisingly, Y1092 phosphorylation of YFP-EGFR-ICD Del746 was still detected in these fibrils (Figure 3C). In line with previous observations [25] the T790M mutation abrogated erlotinib sensitivity. Thus, Akt phosphorylation was readily detected in cells expressing YFP-EGFR-ICD Del746/ T790M, even after treatment with 10 μ M erlotinib.

Testing the kinase activity and erlotinib sensitivity of uncommon EGFR mutants using the YFP-EGFR-ICD assay

We next applied the YFP-EGFR-ICD-based assay to test several uncommon EGFR mutations (Figure 4A) on which limited or no biochemical information is available. These included exon 20 insertions Ins770SVD and Ins774HV, and the exon 21 point mutation P848L, which were detected during our analysis of NSCLC samples (unpublished data). We also tested the exon 21 mutation A859T identified by other groups [28-30].

These mutations were introduced into YFP-EGFR-ICD and transient transfection experiments were carried out in MCF-7 cells. The kinase activity of each mutant (autophosphorylation at Y1092 and phosphorylation of endogenous Akt), and its response to different concentrations of erlotinib were evaluated as described above. Other exon 20 and 21 mutations (T790M, S768I and L858R) that have been previously tested us-

ing transfection-based assays were also included in the assay for comparison.

Among the exon 20 mutations tested, Ins770SVD showed an intermediate level of autophosphorylation, lower than S768I, but higher than T790M (Figure 4B). It was not possible to accurately evaluate autophosphorylation of Ins774HV, since the expression level of this mutant was consistently low in all attempted experiments. Akt phosphorylation was readily detected in cells transfected with S768I, Ins770SVD or Ins774HV, but not in cells expressing T790M (Figure 4B). The phosphorylation of Akt induced by S768I was abrogated by 100 nM erlotinib, and fibril formation was noted upon treatment with 1 μ M or higher concentration of the drug. In contrast, the phosphorylation of Akt induced by Ins770SVD or Ins774HV was only abrogated at the highest concentration of erlotinib tested (10 μ M). In the case of YFP-EGFR-ICD Ins770SVD, 10 μ M erlotinib also induced relocation of the chimeric protein to fibrils. No fibrils were observed in the case of YFP-EGFR-ICD T790M or Ins774HV at any of the erlotinib concentrations tested.

On the other hand, YFP-EGFR-ICD proteins bearing the uncommon exon 21 mutation P848L and A859T showed markedly lower autophosphorylation levels than YFP-EGFR-ICD L858R (Figure 4C). Neither P848L nor A859T were able to induce phosphorylation of endogenous Akt. Erlotinib induced fibrillar relocation of YFP-EGFR-ICD A859T when applied at 10 μ M, but did not have any apparent effect on P848L at any of the concentrations tested. In contrast, YFP-EGFR-ICD L858R induced phosphorylation of endogenous Akt, which was inhibited by 10 nM of erlotinib, and 100 nM or higher concentrations of the drug induced fibril formation. The T790M mutation abrogated the effect of erlotinib on L858R, and the L858R/T790M double mutant readily induced Akt phosphorylation even in the presence of 10 μ M erlotinib.

Discussion

In a subset of NSCLC patients, the presence of somatic mutations in the kinase domain of EGFR may predict the outcome of treatment with the EGFR TKIs erlotinib and gefitinib. The favorable clinical response of tumors harboring the common exon 19 deletions or the L858R mutation correlates with the high TKI sensitivity of these EGFR mutant proteins at the molecular level. However, a large variety of different EGFR mutant alleles have been identified in NSCLC patients, and it is becoming increasingly clear that different EGFR mutants may vary dramatically in their sensitivity or resistance to TKIs [15,31-33]. This issue is of particular importance in the context of ongoing prospective clinical studies in which patient selection is based on the presence of EGFR mutations. In addition, novel treatment options are being explored for those NSCLC patients bearing TKI-resistant EGFR mutations. These options include the use of second-generation irreversible EGFR TKIs currently on development, but might be extended in the future to targeting other components of the pathway.

Evaluating the biochemical characteristics of mutant EGFR proteins using *in vitro* or cell-based assays provides clues to the phenotypical consequences of each alteration. Several relatively uncommon EGFR mutants have been tested in transfection-based assays, using immunoblot with phosphorylation-specific antibodies to assess EGFR activity [15,17-21]. In these studies, a homogeneous population of transfected cells was usually generated, by using viral transduction or by selecting stable transfectants, which are both labor-intensive and time-consuming procedures. We describe here a rapid cellular assay system to evaluate the kinase activity and erlotinib sensitivity of EGFR mutants, using an YFP-tagged fragment of EGFR intracellular domain (YFP-EGFR-ICD) and immunofluorescence. Our assay presents several advantageous characteristics with respect to previously used methods.

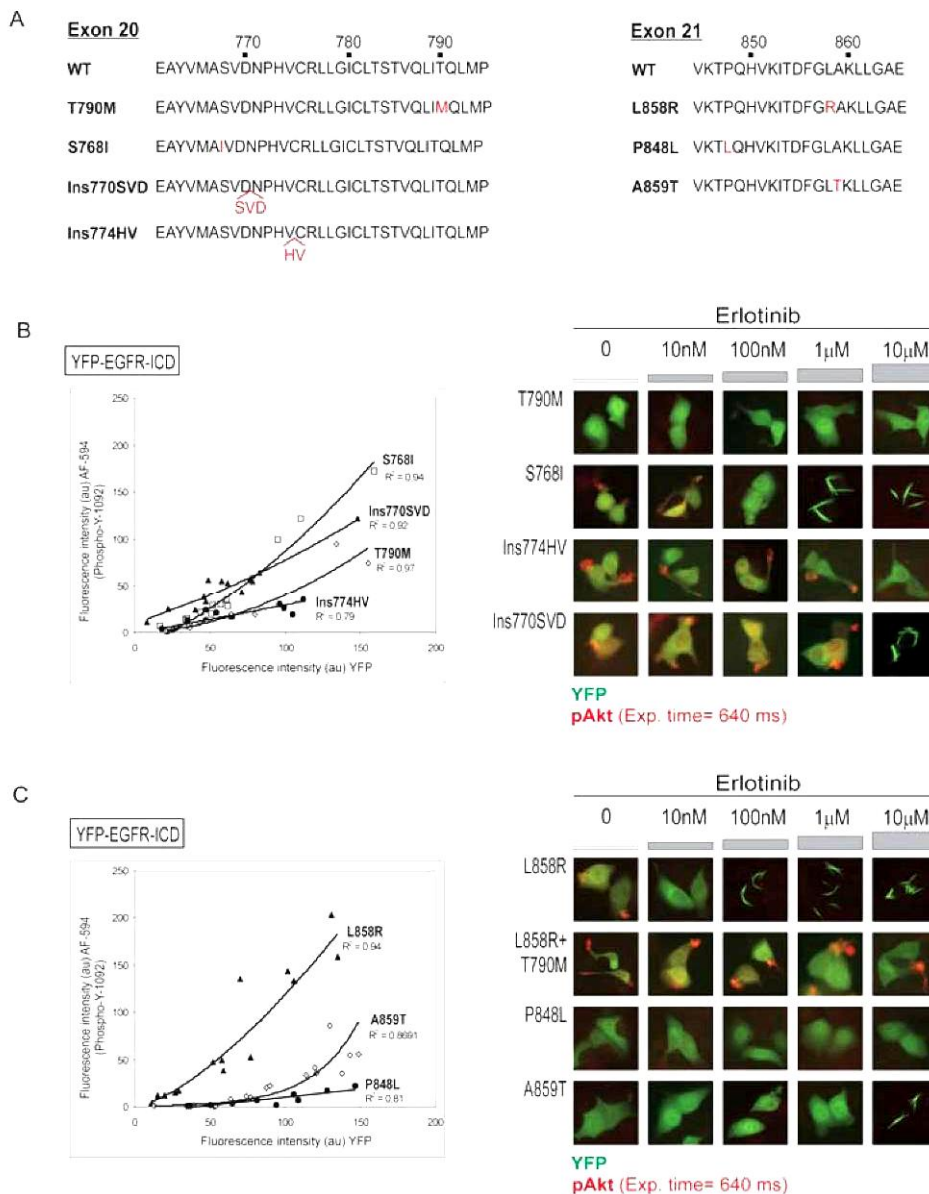


Figure 4. Testing the kinase activity and erlotinib sensitivity of uncommon EGFR mutants using the YFP-EGFR-ICD assay. *A.* Partial amino acid sequence of EGFR exon 20 and exon 21 illustrating the location of the mutations examined (red letters). *B.* Kinase activity and erlotinib sensitivity of different exon 20 mutations. Graph shows that autophosphorylation levels are lower for T790M (white diamonds) than for S768I (white squares) or Ins770SVD (black triangles). Low expression levels hampered the accurate evaluation of Ins774HV (black circles). Images show that YFP-EGFR T790M did not effectively induce phosphorylation of endogenous Akt in MCF-7 cells, and did not relocate into fibrils upon erlotinib treatment. S768I-induced pAkt was inhibited by 100 nM erlotinib and the ectopic protein relocated into fibrils at 1 µM. The phosphorylation of Akt induced by exon 20 insertions was only inhibited at 10 µM erlotinib. This drug concentration also induced relocation of YFP-EGFR-ICD Ins770SVD into fibrils. *C.* Kinase activity and erlotinib sensitivity of different exon 21 mutations. Graph shows that the common L858R mutation confers higher autophosphorylation levels to YFP-EGFR-ICD than P848L and A859T. Images show that, unlike L858R, these uncommon exon 21 mutants did not induce phosphorylation of endogenous Akt. Erlotinib blocked L858R-induced pAkt at 10 nM, and caused relocation of the ectopic protein into fibrils at 100 nM. Both effects were readily abrogated by the TKI-resistant mutation T790M. In all cases, data corresponding to one experiment are shown. Each EGFR mutant was tested at least twice with similar results.

First, by using a fragment of the receptor lacking the extracellular domain one would expect to reduce interference from the experimental context, which may have been partially responsible for some controversial findings [4,6,10,19,20]. Furthermore, the use of a shorter EGFR fragment instead of the full-length receptor renders the mutagenesis procedure more efficient. Finally, by evaluating EGFR activity in a single-cell basis, our assay circumvents the need of a homogeneous population of transfected cells allowing the use of transient transfection. The whole procedure of testing a new EGFR mutant, including site-directed mutagenesis (2 days), verification of the construct by sequencing (1 day), transfection, immunostaining and scoring (3 days) can be completed in approximately one week. In comparison, the generation of a population of stably transfected cells would typically require several weeks of selection in antibiotic-containing medium.

By using the well-characterized EGFR mutant Del746 as control, we demonstrate that the YFP-EGFR-ICD-based assay readily identifies differences between this mutant and the wild type protein in terms of auto-phosphorylation, activation of downstream signaling pathways and sensitivity to erlotinib. We also show that computer-assisted measurement of fluorescence intensity can be used to obtain a semi-quantitative comparison of auto-phosphorylation levels between different mutants. It must be acknowledged that immunofluorescence staining is a less quantitative approach than immunoblot to evaluate protein phosphorylation levels, a disadvantage that is, in our view, counterbalanced by the preservation of cellular morphology. Morphological examination allowed us to observe that phosphorylated endogenous Akt preferentially localizes to membrane ruffles and the tip of lamellipodial protrusions in cells expressing mutant EGFR-ICDs. This observation is consistent with the localization of activated endogenous Akt in growth factor-stimulated cells and its role in cell motility [[34], and references therein].

Microscopy analysis led to the unexpected observation that erlotinib treatment induces the relocation of the YFP-EGFR-ICD chimeric protein to thick cytoplasmic filaments. Importantly, the wild type protein formed fibrils only at 10 μ M erlotinib, whereas the TKI-sensitive mutants relocated to fibrils in the presence of 10–100 nM erlotinib, and this effect was fully abrogated by the erlotinib-resistant T790M mutation. These observations suggest that the relocation of the chimeric YFP-EGFR-ICD protein into thick fibrils at lower drug concentrations is a marker of erlotinib sensitivity in our assay. The molecular basis for this effect of erlotinib is presently unclear. Additional experiments are required, for example, to clarify why YFP-EGFR-ICD Del746 remains phosphorylated (pY1092) in these fibrils in the presence of 500 nM erlotinib, even if downstream signaling (pAkt) is inhibited. We speculate that erlotinib binding to the ATP-binding site in the context of YFP-EGFR-ICD molecule may introduce a conformational alteration sufficient to lead to the aggregation of the chimeric protein. Importantly, we have noted that such effect is not erlotinib-specific, since a similar relocation can be induced by gefitinib treatment (data not shown). It remains to be further examined if fibril formation is a general effect of TKI-mediated EGFR inhibition. In this case, the YFP-EGFR-ICD assay system could be adapted for high content screening of potential anti-EGFR agents, since the shift from a diffuse YFP signal to a fluorescent signal concentrated in thick fibrils would be readily detected using automated image analysis. This possibility is particularly appealing in the context of the currently on-going effort to develop second-generation irreversible TKIs and other agents that may circumvent resistance to TKI associated with the presence of certain types of EGFR mutations.

Over the last three years, we have carried out mutational analysis of EGFR in tumor samples from nearly 300 NSCLC patients [[35,36] and unpublished data]. Several uncommon EGFR mutants identified in the

course of this analysis were tested using the YFP-EGFR-ICD assay.

Mutations in exon 20, most notably T790M, are usually associated with resistance to gefitinib and erlotinib [reviewed in [37]]. We found that Ins770SVD and Ins774HV are more resistant to erlotinib than S768I in our assay. These results are in line with previous data showing increased erlotinib resistance for a similar (Ins770NPG) mutant [15]. Furthermore, our results show that both insertions confer higher kinase activity than T790M, thus underscoring an important difference between these two types of exon 20 alterations. In this regard, there has been some controversy regarding the enhanced kinase activity of T790M-mutant EGFR [22]. We noted that the autophosphorylation level (pY1092) of YFP-EGFR-ICD T790M was indeed higher than that of the wild type protein at lower expression levels (compare graphs in Figure 1D and Figure 4B), as reported by Vikis et al [22]. However, the ability of this mutant to activate downstream signaling was clearly reduced in comparison to the ICD constructs bearing the Del746, L858R, S768I, Ins770SVD or Ins774HV mutations. Recent structural analyses indicate that enhanced activity of EGFR mutants may derive from the disruption of autoinhibitory interactions that suppress EGFR basal activity [23,38]. Our data suggest that exon 20 insertions may disrupt these interactions to a greater extent than the T790M point mutation.

On the other hand, our functional analysis indicates that the uncommon exon 21 mutation P848L is not a kinase-activating mutation and does not confer increased sensitivity to erlotinib. This change has been detected in both tumor and normal tissues from NSCLC patients [[39]; Gallegos-Ruiz et al., unpublished data]. Furthermore, although EGFR and K-ras mutations are in general mutually exclusive in NSCLC patients [37], a K-Ras mutation (G12V) was detected in tumor cells bearing the P848L allele (Gallegos-Ruiz et al., unpublished). Like P848L, the A859T variant, which has been detected in

two nonresponding NSCLC patients [28,29], did not confer increased kinase activity or erlotinib sensitivity in our test. Together, the results from the YFP-EGFR-ICD assay and the clinical behavior of tumors bearing these alterations suggest that P848L and A859T are likely to be uncommon, functionally silent EGFR polymorphisms.

Conclusion

In conclusion, we describe here the use of a simple cellular assay that can be easily implemented to functionally evaluate EGFR variants. The ability to rapidly obtain functional information on EGFR variants of unknown relevance might prove important in the future for the management of NSCLC patients bearing uncommon EGFR mutations. In addition, our assay may be used to determine the response of resistant EGFR mutants to novel second-generation TKIs or to other therapeutic agents targeting the EGFR signaling pathway.

Methods

Plasmid construction and site-directed mutagenesis

In order to generate the YFP-EGFR-ICD construct, a DNA fragment encoding EGFR residues 688–1116 was amplified by PCR using primers TDG1 and TDG4, and full-length human EGFR cDNA (kindly provided by Dr. H. Nakagawa, University of Pennsylvania, Philadelphia) as template. The amplified product was digested with *Hin*-dIII and *Kpn*I and cloned into the pEYFP-C1 mammalian expression vector (Clontech, Palo Alto, CA). NSCLC-associated mutations were subsequently introduced into YFP-EGFR-ICD using the QuickChange II XL Site-Directed Mutagenesis Kit (Stratagene, La Jolla, CA) following manufacturer's protocol. In all cases, the sequence of the inserts was verified by DNA sequence. The sequence of all primers used is available upon request.

Cell culture, transfection and drug treatment

Human breast cancer cells MCF-7 were grown in Dul-becco's modified Eagle's medium (BioWhittaker, Walkersville, MD),

supplemented with 10% fetal calf serum (FCS), 100 units/ml penicillin, and 100 µg/ml streptomycin (Gibco-Invitrogen, Breda, The Netherlands). Cells were seeded onto sterile glass coverslips in twelve-well trays, and transfected with 0.5–1 µg of plasmid DNA using the FuGene6 transfection reagent (Roche Molecular Biochemicals, Almere, The Netherlands), following the manufacturer's protocol. Erlotinib (Roche Pharmaceuticals, Mannheim, Germany) was added at the indicated concentration 4 hours after transfection, and the cells were incubated for 20 hours before being processed for immunofluorescence analysis. Erlotinib treatment was always performed in standard culture medium containing 10% FCS.

Immunofluorescence and microscopy analysis

To evaluate EGFR autophosphorylation, rabbit anti-pEGFR-Y845 (#2231, diluted 1:180) and mouse anti-pEGFR-Y1068 (#2236, diluted 1:180) antibodies were used. Note that the EGFR numbering system used by the manufacturer (Cell Signaling Technology, Danvers, MA) does not include the 24-residue signal peptide. According to the numbering system used in this report, these antibodies recognize residues pY869 and pY1092, respectively. On the other hand, rabbit anti-pAkt-S473 (#9271, diluted 1:100) and rabbit anti-pERK1/ERK2-T202/Y204 (#9101, diluted 1:100) antibodies, both from Cell Signaling Technology, were used to evaluate activation status of EGFR downstream pathways.

The immunostaining procedure was as previously described [40] with minor modifications. Briefly, cells were fixed using 3.7% formaldehyde in PBS for 30 minutes and permeabilized with 0.2% Triton X-100 in PBS for 10 minutes. Following a blocking step with 3% bovine serum albumin in PBS for 1 hour, the primary antibody diluted in blocking solution was applied for 1 hour. After washing with PBS, samples were incubated with Alexa Fluor 594 (AF-594)-conjugated anti-mouse or anti-rabbit secondary antibodies (Molecular Probes-Invitrogen,

Breda, The Netherlands) for 45 min. Finally, the cover-slips were mounted onto microscope slides with Vectashield (Vector, Burlingame, CA). The chromosome stain Hoechst 33285 (Sigma, St Louis, MO) was used to counterstain the cell nuclei.

F-actin staining was carried out by incubating fixed and permeabilized cells with Rhodamine-conjugated phalloidin diluted in blocking solution for 30 minutes (Molecular Probes-Invitrogen, Breda, The Netherlands).

Slides were examined using an inverted Leica DMIRB/E fluorescence microscope (Leica Heidelberg, Heidelberg, Germany). The LeicaQ500MC Quantimet software V01.01 (Leica Cambridge Ltd., Cambridge, UK) was used to collect images, keeping exposure time constant to allow for comparison of signal intensity between different samples. The same software was used to carry out semi-quantitative image analysis of YFP-EGFR-ICD expression level and pY1092 phosphorylation level. To this end, images were acquired using 400 × magnification. A cytoplasmic area was selected (Figure 1D), and the intensity of the fluorescent signal within this region was measured in the green (YFP fluorophore) and the red (AF-594 fluorophore) channels. The intensity of the signal was also measured in a region outside the cell to determine background fluorescence. After subtracting the background, the fluorescence intensity of both fluorophores was plotted against each other using Excel, and the best-fitting trend line (highest R² value) was added using the "Add trend line" feature.

Competing interests

J.A.R. received financial support from Roche during the elaboration of this study. G.G. received research grants from Roche and Astra Zeneca, and was a consultant for both companies.

Authors' contributions

MM dG generated the plasmids and carried out cellular assays. MI G-R sequenced the plasmids and carried out cellular assays. GG participated in the interpretation of the results and the drafting of the manuscript. JAR conceived the study, carried out

experimental work and participated in the interpretation of the results and in the drafting of the manuscript. All authors read and approved the final manuscript.

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FUNCTIONING IN INDIVIDUALS WITH CHRONIC FATIGUE SYNDROME: INCREASED IMPAIRMENT WITH CO-OCCURRING MULTIPLE CHEMICAL SENSITIVITY AND FIBROMYALGIA

Brown M.M., Jason L.A.

Department of Psychology, DePaul University, Center for Community Research, Chicago, IL, USA

Chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS), and fibromyalgia (FM) commonly co-occur. Some propose that CFS, MCS, and FM are manifestations of the same illness based on high rates of co-occurrence and overlapping diagnostic criteria. This study seeks to differentiate these diagnoses by comparing individuals with one or more illness on functioning, psychiatric comorbidity, coping style, and in vivo physical measures.

Participants included 114 men and women who met criteria for CFS. FM was diagnosed during a physical examination, and MCS was assessed using a questionnaire. Participants were divided into four groups: CFS alone, CFS-MCS, CFS-FM, and CFS-MCS-FM. Self-report measures, a psychiatric interview, and in vivo physical measures were given.

43.9% met criteria for CFS alone, 23.7% met criteria for CFS-MCS, 15.8% met criteria for CFS-FM, and 16.7% met criteria for CFS-MCS-FM. The CFS-MCS-FM group was more disabled than the CFS alone group on measures of physical functioning, general health, and bodily pain. In vivo measures did not differ, but the CFS-MCS-FM group rated exertion higher than the CFS alone group.

Individuals with CFS alone were the highest functioning group across several domains, such as disability, depression, and severity of symptoms. Participants with three diagnoses experienced the greatest amount of disability. While substantial co-occurrence of these illnesses was found, this study provides evidence that having more than one illness exacerbates one's disability beyond CFS alone.

Background

Chronic Fatigue Syndrome (CFS) is a debilitating illness affecting approximately .42% of adults in the US [1]. A diagnosis of CFS based on the current US case definition [2] requires at least six months of persistent fatigue along with at least four of eight specified symptoms (e.g., impaired memory and concentration, unrefreshing sleep, post-exertional malaise). Relatively few patients with CFS completely recover from the illness [3], with a recovery rate of 0–6% and increased disability in 10–20% of patients over time [4].

Many of the symptoms associated with CFS are also characteristic of Fibromyalgia (FM) and Multiple Chemical Sensitivity (MCS). FM is a common rheumatologic ailment characterized by chronic generalized muscle pain, fatigue, and disrupted sleep. FM is present in about 3.4% of American women and .5% of men [5]. It has been found to occur following an acute medical illness, a traumatic injury, or surgery [6]. Proposed criteria for the diagnosis of FM require widespread muscular pain in conjunction with tenderness at a minimum number of tender points [7]. CFS and FM often co-occur [8–

10]. It has been estimated that 20–70% of FM patients meet the criteria for CFS, and about 35–75% of patients with CFS also have FM [11–13]. Patients diagnosed with both CFS and FM have been found to be more disabled than those with either condition alone [14], suggesting that co-occurring CFS and FM has an additive effect on disability.

MCS is a commonly diagnosed illness, and is estimated to occur in 6% of adults in California [15]. MCS is defined as a chronic condition with reproducible symptoms involving multiple organ systems; with symptoms that are produced by low levels of exposure to multiple, chemically-unrelated substances and improve or resolve when the chemical agents are removed [16]. Common triggers include pesticides and perfumes [15], causing skin irritation, fatigue, fevers, and neurocognitive dysfunction. Treatment typically involves avoidance of exposure to offending chemicals using such tactics as eliminating carpeting, pesticides and cleaning agents from the home and avoiding other substances experienced as toxic [17]. Chemical avoidance was found to be an effective treatment in 93% of patients [18–20]. MCS is a commonly co-occurring illness with both

CFS and FM. In a sample of 33 Gulf War veterans with CFS, 42% had concurrent MCS and 6% had concurrent FM [21]. Estimated rates of CFS comorbidity in persons with MCS range from 30% to 88% [11,22].

Based on the substantial co-occurrence of CFS, MCS, and FM, it is important to examine the functional status of individuals who experience two or more of these diagnoses. In a tertiary care sample, Ciccone and Natelson [23] found that women with all three diagnoses experienced poorer physical functioning, more pain, and more fatigue than those with CFS only. The study by Ciccone and Natelson is the only one to compare all three illnesses, but males were excluded from their sample. Additionally, that study did not examine stress, coping, quality of life or measures that did not rely on self-report data. The present study explored whether individuals with three illnesses are more disabled than those with two or one, and assessed different coping styles in response to their disability. Additionally, the use of in vivo physical measures was used to supplement information from self-report measures in order to employ multiple methods in gaining a more comprehensive understanding of this illness.

Methods *Participant recruitment*

Participants were recruited from a variety of sources, including physician referrals. Information about the non-pharmacologic treatment trial study was disseminated to medical colleagues through mailings, phone communication, and invited grand rounds. In addition, study announcements for new participants were placed in local newspapers and recruitment offers were made at local CFS support group meetings. These efforts were continued until the target enrollment numbers were achieved. One hundred and fourteen individuals were recruited. All procedures were approved by the DePaul University Institutional Review Board. Informed consent was given by all participants.

Of the 114 individuals, 46% were referred by physicians, 34% were recruited by

media (newspapers, TV, radio, etc.), and 20% stemmed from other sources (e.g., heard about the study from a friend, family member, person in the study, etc.). There were no significant demographic differences for patients recruited from these varying sources. Twenty-four additional individuals who were screened were excluded for various reasons (i.e., lifelong fatigue, less than 4 Fukuda symptoms, Body Mass Index > 45, melancholic depression or bipolar depression, alcohol or substance abuse disorder, autoimmune thyroiditis, cancer, lupus, rheumatoid arthritis). Approaches to reduce attrition included use of letters and telephone reminders of all appointments, flexibility regarding working around vacations and medical and other crises, reimbursement for transportation costs, and participant honoraria.

Initial screening

All participants were required to be at least 18 years of age, not pregnant, able to read and speak English, and considered to be physically capable of attending the scheduled sessions. Patients who were bedridden or used wheelchairs were excluded due to the practical difficulties of making appointments. Referrals to local physicians who treat CFS and to support groups were offered to these individuals. After a consent form was filled out, prospective participants were initially screened by the third author, using a structured questionnaire.

The CFS questionnaire

This screening scale was initially validated by Jason, Ropacki, et al. [24]. This scale is used to collect demographics, health status, medication usage, and symptom data. The CFS Questionnaire was revised, and administered it to three groups: those with CFS, Major Depressive Disorder, and healthy controls [25]. The revised instrument, which was used in the present study, evidences good test-retest reliability and has good sensitivity and specificity.

For each symptom, participants were asked to indicate if the symptom had been present for 6 months or longer, if the symptom began before the onset of their fatigue or

health problems, and how often (never, seldom, often/ usually, or always) the symptom is experienced. Participants were also asked to rate the severity of each symptom they endorsed on a scale of 0 to 100, where 0 = no problem and 100 = the worst problem possible. This is a numerical rating scale (NRS), which has been shown to be a consistently valid measure of symptom intensity, particularly for pain intensity [26]. The Fukuda et al. [2] case definition symptoms (i.e., impaired memory or concentration, sore throat, tender lymph nodes, muscle pain, multiple-joint pain, new headaches, unrefreshing sleep, and post-exertion malaise) were assessed.

A series of questions assessing MCS were included in the CFS Questionnaire. Questions that qualified a diagnosis of MCS included new awareness of odors, frequency of fever (not at all through daily), how sick one would be filling his or her own gas tank (not at all through a lot), and how sick one would be if he or she had to spend four hours in an enclosed shopping mall (not at all through a lot). These questions were derived from Donnay's [27] screening survey for CFS, MCS, and FM. This survey has evidenced diagnostic specificity of 96.7% and specificity of 98.3% (A. Donnay, personal communication, December 1, 2000).

Structured clinical interview for DSM-IV

A semi-structured psychiatric interview was administered. The Structured Clinical Interview for DSM-IV (SCID) [28]. Axis I was used to establish psychiatric diagnoses. The professionally administered SCID allows for clinical judgment in the assignment of symptoms to psychiatric or medical categories, a crucial distinction in the assessment of symptoms that overlap between CFS and psychiatric disorders, e.g., fatigue, concentration difficulty, and sleep disturbance [3]. A psychodiagnostic study [29] validated the use of the SCID in a sample of CFS patients. Because CFS is a diagnosis of exclusion, prospective participants were screened for identifiable psychiatric and medical conditions that may

explain CFS-like symptoms. These measures were completed at DePaul University and took approximately two hours. After the initial interview was completed, the patients' information was reviewed to ensure that they met all eligibility requirements. If an individual was eligible for the study, a medical appointment was set up. Conversely, if an individual was not eligible, alternative treatment options were discussed.

Medical assessment of CFS

The physician screening evaluation included an in-depth medical and neurological history, as well as general and neurological physical examinations. A modified version of the CFS questionnaire was used to rule out other disorders [30]. Relevant medical information was gathered to exclude possible other medical causes of chronic fatigue, including exposure histories to tuberculosis, AIDS, and non-AIDS sexually transmitted diseases. Information on prescribed and illicit drug use was also assessed and recorded. The histories of all symptoms related to CFS were gathered. Laboratory tests in the battery were the minimum necessary to rule out other illnesses [2].

FM was diagnosed by the project physician during the medical assessment. The 1990 criteria from The American College of Rheumatology [7] were used. Participants received a diagnosis of FM if they had mild to severe tenderness in at least 11 out of 18 established tender point sites throughout the body.

Medical Outcomes Study-Short Form-36

(MOS-SF-36). The MOS-SF-36, a 36 item broadly-based self-report measure of functional status related to health, identifies eight health concepts as perceived by the individual. The concepts include Physical Functioning, Role Functioning-Physical, Role Functioning-Emotional, Bodily Pain, General Health, Vitality, Mental Health, and Health Transition [31]. A higher score indicates better health or functioning. Test construction studies for the SF-36 [32,33] have shown adequate internal consistency, discrim-

minate validity among subscales, and substantial differences between patient and non-patient populations in the pattern of scores. The SF-36 has also indicated sufficient psychometric properties as a measure of functional status in a CFS population [34].

Fatigue Severity Scale (FSS)

Krupp, LaRocca, Muir-Nash, and Steinberg's [35] Fatigue Severity Scale was used to measure fatigue. This scale includes 9 items rated on 7-point scales and is sensitive to different gradations of fatigue severity. Most items in the Krupp fatigue scale are related to behavioral consequences of fatigue. Previous findings have demonstrated the utility of the Fatigue Severity Scale to discriminate between individuals with CFS, MS, and primary depression [36]. In addition, the Fatigue Severity Scale was normed on a sample of individuals with MS, SLE, and healthy controls. A study by Taylor, Jason and Torres [37] compared the Fatigue Scale [38] with the Fatigue Severity Scale [35] with a sample of healthy controls and a CFS-like group. Within a CFS-like group, the Fatigue Severity Scale was more closely associated with severity ratings for the eight Fukuda et al. [2] CFS symptoms as well as with functional outcomes related to fatigue.

Beck Depression Inventory (BDI-II)

Because depression is the most commonly diagnosed psychiatric disorder in CFS [39], a quantitative measure of depression severity was used. Depressive symptomatology was measured with the BDI-II [40], a 21-item self-report instrument with well-established psychometric properties. This version of the BDI is more consonant with DSM-IV criteria for major depressive disorder. The BDI-II is the only depression rating scale to be empirically tested and interpreted for both depressed and non-depressed patients with CFS [41]. Also the Beck Depression Inventory has shown sensitivity to treatment changes in two cognitive behavioral treatment studies of CFS [42].

Brief COPE

This inventory assesses how individuals cope with the stress in their lives [43]. It

is derived from the Coping Orientation to Problems Experienced Scale [44], which consists of conceptually distinct problem-focused coping and conceptually distinct emotion-focused coping scales. This instrument has been validated and has adequate reliability. There are 28 items concerning ways of coping, and each is rated on a four point scales (anchor points ranging from not doing the coping strategy to doing it a lot). There are 14 coping methods found in these 28 items; the scales are as follows: Self-distraction, Active coping, Denial, Substance use, Use of emotional support, Use of instrumental support, Behavioral disengagement, Venting, Positive reframing, Planning, Humor, Acceptance, Religion, and Self-blame. There are two items for each of these 14 coping methods; the sum of the two items is the score for that particular coping method. Adequate psychometric properties of this instrument have been found [43].

Brief Pain Inventory

The Brief Pain Inventory [45] was administered to measure the severity of pain and the interference of pain in the patient's life. Higher scores indicate more severe levels of persistent pain and higher levels of interference with functioning. This measure exhibits adequate levels of reliability to assess pain in noncancer samples, with coefficient alphas of .70 and above, also evidences good concurrent validity with other generic pain measures, and has been shown to be sensitive to changes in pain status over time [46].

Pittsburg Sleep Quality Index

Sleep disturbances were examined by using the Pittsburg Sleep Quality Index, which was developed to measure sleep quality in psychiatric research [47]. This Index measures sleep disruptions and sleep quality. There are nineteen questions (on 0–3 scale) which generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global

score, which can range from 0 to 21, with higher scores indicating worse sleep quality.

Actigraph

An actigraph is a small, light-weight, cost-efficient activity monitor that can be worn on the waist. It has a long battery life and can continuously collect data every minute of the day and night for 22 days before its memory is filled to capacity [48]. Unlike most activity monitoring devices, the actigraph is capable of recording movement intensity. The actigraph transduces activity using an accelerometer. An 8-bit analog-to-digital converter quantifies these measurements into 128 levels of positive acceleration and 128 levels of negative acceleration 10 times each second. Integration over the resulting sampling time of 0.1 s in combination with other details provided by Tryon and Williams [48] would result in measurement units of 1.664 milli-g/activity activity count. For simplicity, analog-to-digital (A/D) counts are retained as activity units. The average of 600 absolute A/D values is stored in memory at the end of every minute. Participants wore the actigraph on their waist at all times except for when bathing or sleeping for one week.

Six minute walking test

As an in vivo measure of physical functioning, the six minute walking test [49] was used. The test measures the distance walked during a six minute interval. The test is a useful and reproducible measure of exercise tolerance, provides a simple practical guide to everyday disability, and does not require expensive apparatus [49].

Rating of Perceived Exertion

The Rating of Perceived Exertion (RPE) measures perceived intensity of activity based on bodily sensations such as increased heart rate and breathing [50]. Higher scores indicate higher perceived exertion, with scores ranging from 6 (no exertion) to 20 (maximal exertion). The measure was given at 30 second intervals during the six minute walk test. The RPE has evidenced good reliability and validity, particularly for progressive exercise tests [51].

Sit and reach

In order to gain an assessment of flexibility, we administered the sit and reach test, which is the most widely-used measure of flexibility and a primary component of most physical fitness tests. The test is designed to measure the extensibility of the hamstring muscles and the lower back articulations by evaluating the maximal reach an individual can make in a seated position. This test has excellent test-retest and intra-rater reliability [52].

Hand grip

The hand dynamometer test was administered to measure grip strength in pounds, and is a good measure of loss of work capacity [53]. It is fast, easy to perform, and produces a reliable report that is simple to record [54].

Employment status

This measure of role function consisted of work status (working vs. non-working). Employed included those who were working at least 20 hours per week or in school full-time. Unemployed included those who were retired, working fewer than 20 hours per week, not in school, or part-time student. We also assessed the number that are receiving disability benefits, the number on disability or temporary sick leave, and the number with work limitations due to the illness.

Statistical analyses

Chi-square analyses were conducted between diagnostic groups (i.e., CFS only; CFS-MCS; CFS-FM; CFS-MCS-FM) and all categorical variables including race, gender, work status, marital status, whether or not a participant had children, and presence of psychiatric diagnoses. A series of one-way ANOVAs were performed for continuous variables of age, socioeconomic status, fatigue severity, and disability. To decrease the likelihood of a Type 1 error, Tukey HSD adjustments were made.

Results Diagnostic status

Participants were categorized into four groups based on their diagnostic status of CFS alone; CFS and MCS (CFS-MCS); CFS and FM (CFS-FM); and CFS, MCS, and FM

(CFS-MCS-FM). Of the 114 participants, 50 (43.9%) met criteria for CFS alone, 27 (23.7%) met criteria for CFS-MCS, 18 (15.8%) met criteria for CFS-FM, and 19 (16.7%) met criteria for CFS-MCS-FM.

Sociodemographic characteristics

No significant differences were found across diagnostic categories (CFS alone; CFS-MCS; CFS-FM; and CFS-MCS-FM) for the sociodemographic variables of race, marital status, gender, age, socioeconomic status, or whether or not an individual had children. In regards to demographic characteristics, 16.7 % of the participants were male and 83.3% were female. The average age at baseline was 43.8 years. Regarding ethnicity, 87.7 % were Caucasian, 4.4 % were African-American, 4.4 % were Latino, and 3.5% were Asian-American. As for marital status, 49.1 % were married/living with someone, 33.3 % were single, and 17.6 % were either divorced or separated. In terms of work status, 24.6 % were on disability, 23.7 % were unemployed, 20.2 % were working part-time, 19.3 % were working full-time, 6.1% were retired, 4.4 % were part-time students, .9% were full-time students, and .9 % were working part-time and on disability. In terms of education, 47.4% had earned a standard college degree, 21.8% had a graduate or professional degree, 21.1% had partial college, and 9.7% had a high school/GED degree or less. Regarding psychiatric co-morbidity, 62.3% had a lifetime Axis 1 diagnosis, and 38.6% had a current Axis 1 diagnosis.

Outcome measures

Whether individuals were working or not working was examined across the four groups using χ^2 analyses. There were marginally significant differences across the four groups, χ^2 (3, N = 114) = 7.73, $p=.052$. The CFS alone group had the highest percentage of working (54%), while the CFS-MCS-FM group had the lowest percentage of working (21.1%).

Outcome measures assessing fatigue severity, aspects of disability, pain, sleep, depression, and coping among the four diagnostic categories are presented in Table 1. An

ANOVA was used to compare the four diagnostic groups on the eight scales of the MOS-SF-36. All post hoc tests described below used Tukey HSD. Overall significant differences were found for physical functioning (F (3, 108) = 4.40, $p < .01$), general health (F (3, 107) = 5.83, $p < .001$), social functioning (F (3, 107) = 4.27, $p < .01$), and bodily pain (F (3, 107) = 10.59, $p < .001$). Post hoc tests showed that the CFS-MCS-FM group was significantly more disabled than the CFS alone group on the physical functioning, general health, and bodily pain scales. Individuals with CFS-MCS-FM were also more disabled than individuals with CFS-MCS on the bodily pain scale. The former group revealed more disability on the general health scale than the CFS-FM group. There was a significant difference on the bodily pain scale between the CFS alone group and the CFS-FM group such that individuals with CFS-FM were more disabled by pain than individuals with CFS alone. Individuals with CFS-MCS were significantly more disabled with regards to social functioning than individuals with CFS alone.

An ANOVA was conducted to compare individuals on the Beck Depression Inventory. There was a significant difference in depression scores overall (F (3,107) = 3.20, $p < .05$). Post hoc tests revealed that individuals with CFS-MCS-FM experienced significantly more depression than individuals with CFS alone (see Table 1). However, χ^2 analyses did not yield significant differences in current psychiatric diagnoses (χ^2 (3, N = 114) = 2.71, $p=.44$) or lifetime psychiatric diagnoses (χ^2 (3, N = 114) = .85, $p=.84$) across the four groups.

Findings from ANOVAs also showed significant overall differences in sleep quality (F (3,106) = 4.08, $P < .01$), and fatigue severity (F (3,107) = 3.20, $p < .05$). Post hoc analyses revealed that individuals with CFS-MCS-FM experienced significantly more sleep problems than individuals with CFS alone. Individuals with CFS-MCS were found to have significantly higher fatigue se-

verity than individuals with CFS-FM (see Table 1).

The Brief Pain Inventory examined pain severity and pain interference with functioning. ANOVAs revealed overall significant differences between the four groups on pain severity, $F(3,104) = 11.65, p < .001$. For this dimension, individuals with CFS-MCS-FM experienced significantly higher pain severity than individuals with CFS alone and individuals with CFS-MCS. Additionally, individuals with CFS-FM had significantly more pain severity than individuals with

CFS alone. The interference with functioning dimension also revealed overall significant differences, $F(3, 103) = 12.44, p < .001$. Post hoc analyses revealed that individuals with CFS-MCS-FM had significantly more interference in functioning due to pain than individuals with CFS alone and individuals with CFS-MCS. Both individuals with CFS-MCS and individuals with CFS-FM had significantly more interference in functioning due to pain than individuals with CFS alone (see Table 1).

Table 1. Outcome measures for individuals with CFS alone; CFS-MCS; CFS-FM; or CFS-MCS-FM

Outcome Measure	CFS alone (n = 50)	CFS-MCS (n = 27)	CFS-FM (n = 18)	CFS-MCS-FM (n = 19)
Mean (Standard Deviation)				
MOS-SF-36				
Physical Functioning	53.61 (25.05) ^a	42.50 (19.66)	40.56 (23.69)	32.89 (19.95) ^a
Role-Physical	4.69 (12.27)	3.85 (11.60)	4.17 (12.86)	3.95 (12.54)
Bodily Pain	49.83 (21.88) ^{a,c}	40.62 (21.63) ^b	30.00 (13.18) ^c	21.58 (18.60) ^{a, b}
General Health	36.65 (16.74) ^a	28.75 (15.94)	38.54 (16.62) ^b	19.95 (32.24) ^{a, b}
Vitality	20.73 (15.98)	15.19 (12.84)	19.72 (16.31)	11.32 (9.84)
Social Functioning	46.09 (25.15) ^a	30.29 (21.84) ^a	47.22 (23.70)	30.26 (19.68)
Role-Emotional	56.74 (45.00)	47.44 (45.39)	42.59 (35.80)	57.89 (41.34)
Mental Health	67.08 (16.30)	55.85 (19.35)	66.22 (14.79)	62.11 (18.10)
Brief COPE				
Self Distraction	2.30 (0.87) ^{a, b}	2.91 (0.81) ^b	2.89 (0.88)	3.18 (0.65) ^a
Active Coping	2.97 (0.84)	3.15 (0.83)	3.28 (0.73)	3.10 (0.88)
Denial	1.41 (0.85)	1.28 (0.59)	1.25 (0.35)	1.32 (0.61)
Substance Use	1.15 (0.47)	1.22 (0.63)	1.53 (0.98)	1.24 (0.42)
Emotional Support	2.40 (0.95)	2.17 (0.91)	2.56 (0.97)	2.29 (0.85)
Instrumental Support	2.32 (0.96)	2.61 (0.93)	2.78 (0.75)	2.66 (0.99)
Behavioral Disengagement	1.33 (0.51)	1.27 (0.38)	1.47 (0.44)	1.47 (0.94)
Venting	1.93 (0.63)	2.09 (0.77)	2.39 (0.65)	2.11 (.077)
Positive Reframing	2.20 (1.06)	2.28 (0.94)	2.75 (0.96)	2.53 (1.05)
Planning	2.97 (0.97)	3.00 (0.98)	3.00 (0.86)	3.03 (0.86)
Humor	1.68 (0.79) ^a	1.78 (0.87)	2.39 (1.20) ^a	1.79 (0.77)
Acceptance	2.95 (0.88)	2.81 (0.83)	2.94 (0.75)	2.95 (0.80)
Religion	2.41 (1.01)	2.44 (0.97)	2.31 (1.06)	2.47 (1.05)
Self Blame	1.69 (0.87)	1.74 (0.75)	2.00 (0.77)	1.92 (0.79)
Beck Depression Inventory	16.47 (8.61) ^a	20.88 (9.64)	18.50 (9.54)	23.93 (11.43) ^a
Fatigue Severity Scale	5.98 (0.68)	6.35 (0.66) ^a	5.70 (1.22) ^a	6.30 (0.53)
Pittsburgh Sleep Quality Index	7.26 (2.53) ^a	8.69 (2.20)	8.94 (2.10)	8.95 (2.39) ^a
Brief Pain Inventory				
Interference	2.83 (2.52) ^{a, c,d}	4.56 (2.78) ^{b, c}	5.36 (1.96) ^d	6.80 (2.33) ^{a, b}
Severity	3.03 (2.06) ^{a, c}	4.06 (2.02) ^b	4.86 (1.40) ^c	6.10 (2.04) ^{a, b}
Symptoms				
Sore Throat	23.50 (26.61)	29.48 (26.97)	20.56 (26.40)	24.84 (28.82)
Tender Lymph Nodes	25.75 (30.36)	23.40 (26.33)	27.50 (33.79)	32.00 (27.92)
Muscle Pain	50.52 (28.34) ^{a, b}	60.76 (28.22)	72.92 (22.56) ^b	78.42 (24.97) ^a
Joint Pain	31.85 (33.25) ^{a, c}	46.04 (35.95) ^b	63.06 (32.18) ^c	75.50 (24.54) ^{a, b}
Impaired Memory	62.96 (25.22)	59.63 (23.82)	65.14 (25.53)	68.94 (22.65)
Unrefreshing Sleep	76.89 (18.89)	75.19 (25.43)	89.67 (10.86)	87.03 (14.46)
Post-Exertional Malaise	73.27 (17.84)	75.19 (19.16)	74.86 (23.74)	82.36 (14.10)
Headaches	42.91 (33.39) ^a	56.87 (30.50)	55.00 (31.44)	74.03 (24.39) ^a
Six Minute Walk Test				
Distance Walked (feet)	1419.47 (312.17)	1728.08 (2387.62)	1304.28 (356.492)	1221.39 (239.23)
Average RPE	9.85 (2.24) ^a	10.56 (2.08)	11.37 (2.76)	11.78 (2.42) ^a
Sit and Reach (inches)	13.48 (3.54)	13.16 (4.49)	14.55 (4.24)	13.40 (3.77)
Hand Grip (pounds)				
Right	64.45 (24.67)	61.57 (21.21)	64.19 (21.87)	52.28 (15.34)
Left	60.04 (22.71)	58.63 (17.90)	58.72 (20.71)	48.07 (17.21)
Actigraphy Mean	161.35 (58.55)	145.74 (58.13)	167.23 (48.51)	149.78 (63.12)
Lifetime Axis I Diagnosis %	21 (42.0%)	10 (37.0%)	6 (33.3%)	6 (31.6%)
Current Axis I Diagnosis %	17 (34.0%)	5 (18.5%)	7 (38.9%)	6 (31.6%)

Similar letters across diagnostic groups significantly differ at the $p < .05$ level.

For the scales measuring coping, two revealed overall significant differences, including self distraction ($F(3,106) = 6.59, p < .001$) and humor ($F(3,107) = 2.90, p < .05$). Individuals with CFS-MCS, and individuals with CFS-MCS-FM used significantly more self distraction than individuals with CFS alone. Individuals with CFS-FM used significantly more humor as a coping style than individuals with CFS alone (see Table 1).

ANOVAs were also conducted for severity of the eight core CFS symptoms. There were significant group differences for muscle pain ($F(3,109) = 6.19, p < .001$), joint pain ($F(3,110) = 9.96, p < .001$), unrefreshing sleep ($F(3,107) = 3.33, p < .05$), and headaches ($F(3,108) = 4.62, p < .01$). Table 1 shows the group differences based on post hoc analyses. The CFS-MCS-FM group reported significantly more severe muscle pain, joint pain, and headaches than the CFS alone group. They also reported significantly more joint pain severity than the CFS-MCS group. The CFS-FM group reported significantly higher severity of muscle pain and joint pain than the CFS alone group.

No significant differences were found across diagnostic groups for physical measures including the six minute walk test, sit and reach, hand grip strength, and actigraphy. Outcomes for physical measures are reported in Table 1. During the six minute walk test, RPE was calculated every 30 seconds. Mean RPE scores were calculated, and overall significant differences were found between groups ($F(3, 102) = 3.65, p < .05$). Post hoc analyses revealed that the CFS alone group had a significantly lower RPE score than the CFS-MCS-FM group.

Discussion

These results suggest that a substantial number (56%) of patients with CFS also meet criteria for MCS, FM, or both. These findings are consistent with previous research indicating high rates of overlap among these illnesses [11,23]. While some argue that distinguishing between these three syndromes is not merited due to high rates of co-occurrence and overlapping symptom criteria

[55], we found a general pattern indicating that individuals with all three diagnoses experience more overall difficulties when compared to individuals with two or fewer diagnoses. Participants with CFS-MCS-FM experienced more depression and poorer sleep quality than those with CFS alone. They also had poorer physical functioning, more bodily pain, and poorer general health than those with CFS alone. Those with all three diagnoses also had lower general health scores than those with CFS-FM, and more bodily pain than those with CFS-MCS.

In addition, the CFS-MCS group had lower social functioning scores on the SF-36 than those with CFS alone. Our findings regarding the two groups that included individuals with MCS (CFS-MCS and CFS-MCS-FM) are consistent with previous research suggesting that individuals with MCS tend to have low scores on the SF-36 health status scales [56]. Of note, the two MCS groups also utilized self-distraction as a coping mechanism more than the CFS alone, as measured by the Brief Cope. Self-distraction is considered a maladaptive coping style on this measure [57]. It has been hypothesized that individuals with MCS may consider chemical exposure to be unavoidable, leading them to utilize passive coping [58]. Lower social functioning of these individuals and a passive coping style may be a consequence of not being able to avoid chemical exposure.

Although pain is a symptom associated with CFS, it is the hallmark symptom of FM. The two groups that included individuals with FM (CFS-FM and CFS-MCS-FM) reported more bodily pain on the SF-36 than the CFS alone and CFS-MCS groups. Individuals with FM also reported more pain severity and pain interference than the non-FM groups. Additionally, among the eight core symptoms of CFS, they reported more severe headaches, muscle pain, and joint pain than the other groups. This suggests that although many symptoms relating to pain overlap among the disorders, pain-related symptoms are more salient among patients with FM.

High rates of psychiatric comorbidity have been found in studies of patients with CFS, MCS, and FM [59]. Our sample had rates of current psychiatric diagnosis ranging from 18.5% for the CFS-MCS group to 38.9% for the CFS-FM group. In contrast to Ciccone and Natelson [23], we did not find significant differences between groups with regards to psychiatric illness. However, the CFS-MCS-FM group had the highest depression scores, suggesting that depression may be more prevalent in individuals who are living with more severe disability.

We did not find differences between groups for the in vivo physical measures of strength, exercise tolerance, and flexibility. This is in contrast to the various differences found on self-report measures related to physical functioning and disability. Of note, the CFS-MCS-FM group rated a significantly higher level of exertion on the six minute walk test than the CFS alone group. It is possible that the six minute walk test was not strenuous enough to detect differences in performance across groups, but RPE scores suggest that the task was more difficult for the CFS-MCS-FM group. Future research might examine these differences during a higher-intensity activity.

Conclusion

It is important to note that all participants in this study met diagnostic criteria for CFS; so many symptoms were expected to be present across all participants. Individuals with CFS alone were the highest functioning group across several domains, such as disability, depression, and severity of symptoms. In contrast, participants with CFS-MCS-FM experienced the greatest amount of overall disability. However, physical measures of disability were not consistent with these findings, as there were no differences across groups. Individuals with all three diagnoses found the six minute walk test to be more intense, as measured by RPE, compared to the CFS alone group. This study provides evidence that having more than one diagnosis exacerbates one's disability above and beyond CFS alone.

Competing interests

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

Authors' contributions

MB and LJ both conceived of the study. MB carried out the statistical analyses and contributed to the writing of the manuscript. LJ participated in the design of the study and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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DISSECTION AND HEMOSTASIS WITH HYDROXYLATED POLYVINYL ACETAL TAMPONS IN OPEN THYROID SURGERY

Dionigi G., Boni L., Rovera F., Dionigi R.

*Department of Surgical Sciences, University of Insubria,
Viale Borri 57, 21100 Varese, Italy*

The essential objectives for thyroidectomy are: avoidance of injury to the recurrent laryngeal nerves, conservation of the parathyroid glands, an accurate haemostasis and an excellent cosmesis. In the last 10 years major improvements and new technologies have been proposed and applied in thyroid surgery; among these mini-invasive thyroidectomy, regional anaesthesia and intraoperative neuromonitoring, and new devices for achieving dissection and haemostasis. Minor bleeding from small vessels could be a major complication in thyroid surgery. The purpose of ligating vessels is to maintain the surgical site free from an excess of blood and reduce blood loss in the patient.

Hydroxylated polyvinyl acetal tampons (HPA) are made by a synthetic, open cell foam structure able to absorb fluids up to 25 times the initial weight. We tested their efficacy for small bleeding control and tissue dissection during several thyroid procedures.

HPA tampons have been found extremely useful to absorb blood coming from minor and diffuse loss, helping to control bleeding by a combined action of fluid absorption and local compression. The porous design of the tampon allows the use of the suction device right through the tampon itself. Thanks to the initial mildly hard consistency, we also used HPA tampons as dissecting instruments.

In our experience the use of HPA tampons resulted extremely efficient for minor bleeding control, fluids removal and tissue dissection during thyroid surgery.

Background

New technologies have been proposed and applied in thyroid surgery, such as the mini-invasive video-assisted thy-roidectomy (MIVAT) and the intraoperative monitoring of recurrent laryngeal nerve (RLN) [1,2]. In general the essential objectives for thyroidectomy are: conservation of the parathyroid glands, avoidance of injury to RNL, an accurate hemostasis and an excellent cosmesis. The thyroid has a rich blood supply. Each must be securely occluded and divided to perform a safe and expeditious operation [3]. Theodor Kocher is credited with refining the technique of thyroidectomy and reducing the incidence of postoperative hemorrhage [3]. It is difficult to estimate the real impact of bleeding, as main cause of intra-operative accidental lesions of vital structures as RLN [3]. However any surgeon who has routinely been practising thyroid surgery, knows that even minor bleeding may greatly compromise the view of surgical field and lead to severe difficulties in identifying the anatomical structures. Furthermore, management of abnormal bleeding exposes the patient to the morbidity of re-operation. In mini-invasive thyroidectomy intraoperative bleeding is a frequent cause for conversion to open technique [2]. Several devices and techniques,

coming from general surgery, are commonly used to control bleeding, during thyroid surgery. Haemostasis in thyroid surgery is achieved by means of conventional clamp-and-tie technique, diathermy, and haemostatic clips and, more recently, by ultrasonic coag-ulating-dissection and electrothermal bipolar vessel sealing systems. We tested hydroxylated polyvinyl acetal tampons (HPA), their efficacy for small bleeding control and tissue dissection during several thyroid procedures.

Materials and methods *Tampons*

We tested the use of hydroxylated polyvinyl acetal (HPA) tampons (Merocel™ – Medtronic Xomed, Jacksonville, Florida, USA) for minor bleeding control, fluid absorption and dissection during thyroid procedures. Hydroxy-lated polyvinyl acetal tampons are made of synthetic molecule obtained by "foaming at open cell" a fully biocompatible nonirritating polymer. This manufacturing procedure allows the generation of a cellular net made by pores, which are joined together in order to prevent breaks or lost of fibers. They are designed in different shapes, forms and sizes. Specific test demonstrated that HPA tampons are fully biocompatible and able to reduce bacterial grown. Their surface is smooth and they do not stick

to tissues. They have an initial, mildly hard, firmness that allows their use as blunt dissection devices. Once in contact with fluids, the polymeric structure provides great absorbing capacity (up to 25 times the original weight) within a small volume of material. Mero-cel™ tampons are routinely used for removal of unwanted fluids from the operative field in general, neurosurgical operations and for nasal packing in the treatment of epistaxis [4,5,8-10].

Clinical experience

From August 2004 till December 2005, HPA tampons have been used, on demand, in 50 different thyroid procedures (Table 1, 2).

Table 1. Clinical experience with HPA tampons

Thyroid procedure with HPA tampon	Number
Total thyroidectomy	43
Emithyroidectomy	7
TOTAL	50

In 47/50 (94%) cases only one tampon was required, in 3/50 (6%) patients required 2 tampons. This fact is mainly related to the thyroid volume and length of the procedure. The present study did not include cervical lymph node dissections or miniinvasive thyroid procedures.

Table 2. Final pathology

Thyroid procedure with HPA tampon	Number
Nontoxic Goiter	31
Graves' Disease	15
Differentiated Thyroid Carcinoma	4
TOTAL	50

Results

HPA has been used for both benign and malignant thyroid disease, for hemithyroidectomy as well as for total thyroidectomy (Table 1, 2). HPA tampons have been found extremely useful to absorb blood coming from minor and diffuse losing, caused by dissection of tissues, adhesions and small vessel. Once in contact with the bleeding area, HPA tampons are able to expand quickly, helping to control bleeding by a combined

action of fluid absorption and local compression, that facilitates platelets aggregation. Once expanded, the tampon becomes soft and a traumatic and it can be used as gentle retracting and dissecting instrument reducing the risk of accidental damaging.

In a previous laboratory test we found than 1 cm² of HPA tampon was able to absorb a significantly greater amount of blood than the same surface of standard surgical swab; it has also been found that HPA tampons were able to absorb fluids up to 25 times their initial weight [4]. The porous design of the tampon allows performing an effective aspiration of blood and unwanted fluid, by positioning the tampon directly on the bleeding surface (for example close to RNL) and using the suction device right through the tampon itself (Fig. 1). Thanks to the initial hard consistency, we also used HPA tampons as dissecting instruments during thyroidectomy. This resulted extremely useful for the dissection of the thyroid gland from the trachea and muscles, to identify and isolate the RLN or for blunt dissection and taking down of adhesions. In total thyroidectomy, the tampon was left in situ while performing the controlateral emithyroidectomy. Furthermore, opposite to standard pledgets, HPA tampons are totally fibers free and extremely resistant to strong tractions. Their cost is also fairly low (less than 10€ per tampon).

No postoperative mortality or morbidity in these short series was observed. None of the patients showed evidences of allergic reactions or intolerance; no accidental rupture or intra-abdominal lost of tampons were reported.

Conclusion

The use of local haemostatic devices is spread in general surgery to assist in the control of capillary, venous, small arterial haemorrhage and "oozing" bleeding when ligation or other conventional methods of control are impractical or ineffective. New modalities for the haemostasis and dissection in thyroid surgery include clips, tampons, harmonic scalpel, fibrin sealant, electrothermal bipolar vessel sealing system and gauzes. The ef-

fect of a combination of new haemostatic devices on the treatment of dissection and bleeding in thyroid surgery aim to improve primary and secondary haemostasis rates and the safety of treatment [6]. There are no data in Literature of the use of HPA in thyroid surgery in particular open thyroidectomies. Their easy application, low cost, and significant blood-loss reduction make these agents attractive also for thyroid surgery. The use of the haemostats has been approved by the U.S. Food and Drug Administration. In our experience HPA have been documented to be a safe device in open surgery.



Figure 1. Minor bleeding control using HPA tampon, during thyroidectomy. The porous design of the tampon allows performing an effective aspiration of blood and unwanted fluid, by positioning the tampon directly on the bleeding surface (for example, close to RNL) and using the suction device right through the tampon itself.

During thyroid procedures the tampons are cut to the appropriate size for the placement, with a sterile technique in the beginning phases of surgery. The device may be adjusted in the irregular surfaces of the dissecting area between the trachea and the strap muscles thus protecting the RLN from the suctioning drainage. The haemostat, by swelling, may exert pressure resulting in paralysis and/or nerve damage: the hypothesis that these surgical medicaments placed in close proximity to the RLN could be responsible for some postoperative disturbances and that any alteration in nerve function that oc-

curs postoperatively is usually attributed to the trauma of the surgical procedure rather than the medicament is quite difficult to determine. The surgical sponge has a pH of 6.5 ± 1.0 and should not be placed adjacent to neural tissue. Despite this advice it is often placed in direct contact with neural tissue, particularly in neurosurgery. Loescher and Robinson examined the response of tissue to different haemostatics agents left in situ in particular the neural function was reported [7]. The immediate effect of the haemostat on neural function was rare and variable, responsible for some postoperative disturbances, but the effects of these haemostats on neural function were only temporary. We suggest in patients with haemorrhagic disorders, those requiring oral anticoagulant therapy, with persistent major bleeding after primary haemostatic measures during thyroid surgery, hemostasis can be achieved through these new devices. These new devices achieve rapid haemostasis, they must be used in combination but must be used in conjunction with a meticulous surgical technique. The clips and conventional clamp-and-tie technique ideally are suited to acute bleeding and are most effective when a vessel from a bleeding source can be identified. These surgical sponges are not intended as substitutes of careful surgery, a proper use of sutures and ligatures and must never be used to control haemorrhage from large arteries. Specific experience and training with these new devices is essential for optimal use. Preliminary experience using HPA has been encouraging, but prospective randomized trials using adequate patient numbers are still needed to validate efficacy and safety.

Competing interests

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

Authors' contributions GD: acquisition of data

FR: study conception and design

LB: analysis and interpretation of data

GD: drafting of manuscript

RD: Critical revision and supervision

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NON-INVASIVE MR IMAGING OF INFLAMMATION IN A PATIENT WITH BOTH ASYMPTOMATIC CAROTID ATHEROMA AND AN ABDOMINAL AORTIC ANEURYSM: A CASE REPORT

Howarth^{1,2} S.P., Tang^{1,3} T.Y., Graves¹ M.J., U-King-Im¹ J.-M., Li¹ Z.-Y., Walsh³ S.R., Gaunt³ M.E., Gillard¹ J.H.

¹University Department of Radiology, Cambridge University Hospitals NHS,
²Academic Department of Neurosurgery, Cambridge University Hospitals NHS,
³Cambridge Vascular Unit, Cambridge University Hospitals NHS,
 Foundation Trust, UK

Inflammation is a recognized risk factor for the vulnerable atherosclerotic plaque.

USPIO-enhanced MRI imaging is a promising non-invasive method to identify high-risk atheromatous plaque inflammation in vivo in humans, in which areas of focal signal loss on MR images have been shown to correspond to the location of activated macrophages, typically at the shoulder regions of the plaque. This is the first report in humans describing simultaneous USPIO uptake within atheroma in two different arterial territories and again emphasises that atherosclerosis is a truly systemic disease. With further work, USPIO-enhanced MR imaging may be useful in identifying inflamed vulnerable atheromatous plaques in vivo, so refining patient selection for intervention and allowing appropriate early aggressive pharmacotherapy to prevent plaque rupture.

Background

It is accepted that vulnerable atheromatous plaque has a thin fibrous cap and large lipid core with associated inflammation [1]. This inflammation can be detected on Magnetic Resonance (MR) imaging using Ultra Small Super-Paramagnetic Iron Oxide (USPIO) particles as a contrast medium (Sinerem™). This has been validated against the histological gold standard in previous work [2]. Ex-vivo imaging of atheroma allows an extended imaging-time thereby permitting greater signal-to-noise and improving plaque characterisation. This has been shown to correlate well with in-vivo imaging.

Case Presentation

A 72-year old male was referred to the vascular outpatient clinic with an asymptomatic right carotid bruit, for work up before planned coronary artery bypass grafting. His duplex ultrasound showed a 70–80% stenosis of the right internal carotid artery. He was found also to have an incidental 5.6 cm infrarenal abdominal aortic aneurysm (AAA). He underwent multi-sequence MR imaging pre- and 36 hours post USPIO infusion. Multi spectral imaging was acquired at 1.5 Tesla using a whole body system (GE Medical Sys-

tems, Milwaukee) and a custom designed 4-channel phased array neck coil (Flick Engineering Solutions BV) along with a standard body coil to improve signal to noise ratio. The patient subsequently (24 hours) underwent a right carotid endarterectomy and was discharged home after an uncomplicated hospital stay of three days.

The ex-vivo specimen was kept fresh and immersed in an MR inert fluid (Fomblin, Performance Fluids Ltd, UK) and imaged in a dedicated single channel micro-coil 4 hours after surgery. Following this, the specimen was washed, fixed in formalin and embedded in paraffin wax. The paraffin block was divided into 3 mm sections and thin sections were cut from each block. These sections were stained using various techniques including haematoxylin and eosin (H&E) and elastin Van Giesen (EVG). This histology was co-registered with the ex-vivo and in-vivo MR using the bifurcation as a point of reference. There were no problems with the co-registration of the in-vivo images with the ex-vivo images or the histology (see Figure 1).

An elective endovascular repair of his AAA has been scheduled.

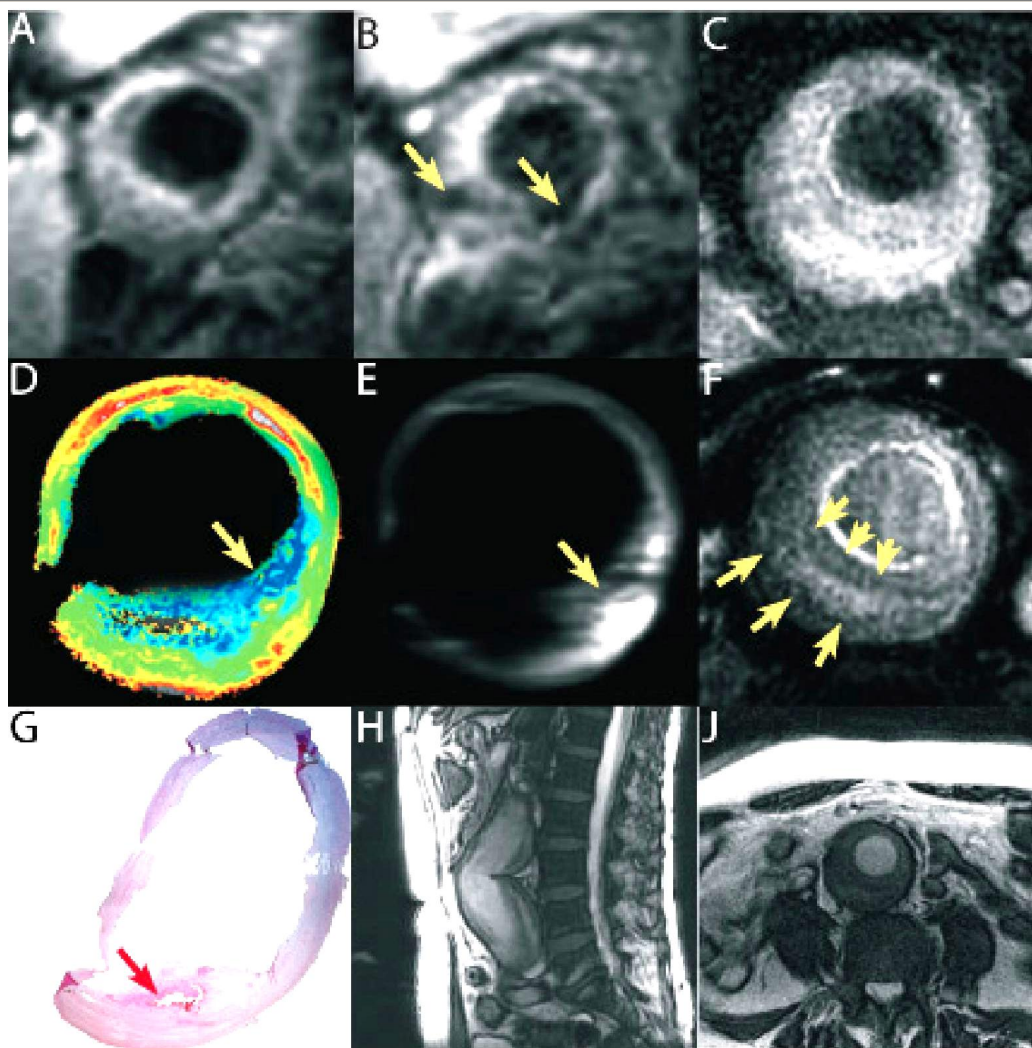


Figure 1. T₂* weighted spiral imaging of the right common carotid artery *in-vivo*, pre (A) and 36 hours post USPIO infusion (B) showing signal loss in areas of USPIO uptake (yellow arrows). (The 2D T₂* weighted spiral acquisition used a spectral-spatial excitation pulse, with a TE of 5.6 ms. The multi-shot spiral sequence involved the acquisition of 22 spiral interleaves each of 4096 data points resulting in an effective in-plane pixel size of 0.42 × 0.42 mm, two signal averages were performed and a quadruple inversion preparation was utilised to null the signal from blood pre – and post USPIO. Slices were acquired sequentially with a 3 mm thickness and no inter-slice gap.). Pre (C) and 36 hours post USPIO infusion (F) T₂* weighted spiral imaging *in-vivo* revealing signal drop in the wall of the aneurysm post-USPIO (yellow arrows) likely corresponding to regions with a high inflammatory burden. Corresponding *ex-vivo* imaging in a dedicated micro-coil with T₂ map (D) showing regions with very short T₂ species (yellow arrow) corresponding with area of USPIO uptake. Ex-vivo inversion recovery on-resonance water suppression (IRON) imaging [9] (E) with off-resonant spins showing positive contrast due to dephasing of spins adjacent to USPIO uptake. H&E section (x40) co-registered with ex-vivo imaging (using distance from the bifurcation). Area of intraplaque haemorrhage within a small necrotic lipid core can be seen (red arrow), adjacent to the USPIO uptake seen in the ex-vivo imaging. Structural MR Imaging in the same patient reveals anatomy of the co-existing abdominal aortic aneurysm (H&J).

Conclusion

Treatment decisions for surgical intervention in patients with asymptomatic carotid atheroma remain controversial. Conventional clinical risk assessment of carotid atheroma is based currently on luminal stenosis alone

[3]. Although important, methods used to measure luminal stenosis such as conventional x-ray angiography and CT angiography do not adequately reflect disease severity in carotid atherosclerosis. They do not permit assessment of the morphology and inflamma-

tory infiltrate of the lesion, which are all recognised risk factors for the vulnerable carotid atheromatous plaque [4]. Furthermore, the process of expansive arterial remodelling [5] may produce normal luminal measurements despite a large atheromatous plaque burden in a particular patient and therefore underestimate their risk of stroke.

USPIO-enhanced MRI imaging is a promising non-invasive method to identify high-risk atheromatous plaque inflammation in vivo in humans, in which areas of focal signal loss on MR images have been shown to correspond to accumulation of iron particles in ex vivo specimens [2,6]. USPIO is thought to accumulate predominantly in activated macrophages either at the shoulders or in the necrotic lipid core of ruptured and rupture-prone human atherosclerotic lesions and is considered to be a marker of the degree of inflammation within the plaque [7,8].

This is to the authors' knowledge the first report in humans describing simultaneous USPIO uptake within atheroma in two different arterial territories and again emphasises that atherosclerosis is a truly systemic disease.

With further work, USPIO-enhanced MR imaging may be useful in identifying inflamed vulnerable atheromatous plaques in vivo, so refining patient selection for intervention and allowing appropriate early aggressive pharmaco-therapy to prevent plaque rupture. It may also prove a

useful adjunct in the identification of inflammation within other vascular beds such as in the detection of inflammatory abdominal aortic aneurysms, which may contribute to surgical decision making in the future.

Competing interests

JHG is a consultant to GlaxoSmithKline

Authors' contributions

SH jointly had the original idea, drafted the manuscript and designed the Figure. TT jointly had the original idea, was involved in the drafting and editing of the manuscript and Figure. MJG carried out the MR sequence development and helped in drafting the ma-

nuscript. JMUKI participated in the design of the study and edited the manuscript. ZYL helped in editing the manuscript and creating the Figure. SRW was involved with manuscript editing, patient care and helped perform the operation. MEG edited the manuscript, was the clinical lead in the patient's care and was the primary surgeon in performing the carotid endarterectomy. JHG helped conceive the study, was involved in the radiology reporting of the patient's MR images and edited the manuscript. All authors have read and approved the final manuscript.

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DUKE SURGERY PATIENT SAFETY: AN OPEN-SOURCE APPLICATION FOR ANONYMOUS REPORTING OF ADVERSE AND NEAR-MISS SURGICAL EVENTS

Pietrobon¹ R., Lima¹ R., Shah¹ A., Jacobs² D.O., Harker² M., McCready¹ M., Martins¹ H., Richardson³ W.

¹*Center for Excellence in Surgical Outcomes, Department of Surgery, Duke University Medical Center, DUMC 3094, Durham, NC 27710, USA,*

²*Department of Surgery, Duke University Medical Center, DUMC 3704, Durham, NC 27710, USA,*

³*Division of Orthopaedic Surgery, Department of Surgery, Duke University Medical Center, DUMC 3077, Durham, NC 27710, USA*

Studies have shown that 4% of hospitalized patients suffer from an adverse event caused by the medical treatment administered. Some institutions have created systems to encourage medical workers to report these adverse events. However, these systems often prove to be inadequate and/or ineffective for reviewing the data collected and improving the outcomes in patient safety.

To describe the Web-application Duke Surgery Patient Safety, designed for the anonymous reporting of adverse and near-miss events as well as scheduled reporting to surgeons and hospital administration.

Software architecture: DSPS was developed primarily using Java language running on a Tomcat server and with MySQL database as its backend.

Formal and field usability tests were used to aid in development of DSPS. Extensive experience with DSPS at our institution indicate that DSPS is easy to learn and use, has good speed, provides needed functionality, and is well received by both adverse-event reporters and administrators.

This is the first description of an open-source application for reporting patient safety, which allows the distribution of the application to other institutions in addition for its ability to adapt to the needs of different departments. DSPS provides a mechanism for anonymous reporting of adverse events and helps to administer Patient Safety initiatives.

The modifiable framework of DSPS allows adherence to evolving national data standards. The open-source design of DSPS permits surgical departments with existing reporting mechanisms to integrate them with DSPS. The DSPS application is distributed under the GNU General Public License.

Background

Anonymous reporting of adverse and near-miss events

Near miss events occur in every medical facility all over the world. Studies have shown that 4% of hospitalized patients suffer from an adverse event caused by the medical treatment administered [1,2]. These mistakes can result in patient discomfort, irreversible injury, or even death. Although patient safety is a topic of major emphasis for medical facilities, efforts to investigate the causes and prevention of these errors have been insufficient, reflecting a general lack of awareness of the problem [2]. As a consequence of this oversight, the need for effectively collecting and understanding data about these adverse events is paramount in improving patient safety. Some institutions have created systems to encourage medical workers to report these adverse events so that they may be

formally documented and reviewed. However, these systems have often proven to be inadequate or ineffective for reviewing the data collected and improving the outcomes in patient safety. Studies on the handling of incident reports indicated that no clear and consistent methodology across a number of organizations were of an appropriate added value to patient safety mechanisms [1].

Existing approaches

Although systems have been created for reporting adverse events, there does not exist, to the best of our knowledge, an open source application for reporting patient safety. The open source application is a software system that permits the usage and modification of its source code. In laymen's terms, "open-source," by definition, implies that the software allows anyone to improve, redistribute, and share it with others [3-8]. There are a number of Web-based event reporting sys-

tems in health care. US Pharmacopeia's MedMarx system [9] and the Institute for Safe Medication Practices' Medication Errors Reporting Program [10] collect data on medication errors. The Emergency Care Research Institute (ECRI) [11] collects reports of adverse events involving medical products. Mekhjian et al recently implemented a voluntary reporting system that collects data about errors, events, and near misses solely at Ohio State University. All of these systems focus on a specific type of event (e.g., medications) or are localized at one institution. While virtually all medical institutions have some in-hospital mechanism for reporting incidents, typically these systems are mandatory and non-anonymous. This allows blame to be focused on individuals, and, as a result, these systems result in grave underreporting.

A single-institution study found that a significant increase in reporting occurred within the first year of a hospital-wide implementation of a Web-based electronic safety event reporting system [12]. Twenty-two percent of the safety events reported resulted in patient harm; 16% of these were near misses. Nurses entered 73% of the events and physicians only 2%. Miscoding of event details and underreporting were common. Most of the events were reported by nurses [12] which highlights the need of a system that allows all staff, including physicians and other team members, involved with patient care to report incidents. At the same time, more than one report may be submitted for the same episode and the system must be prepared to identify such cases. These results suggest that more work is needed to involve care team members in reporting, improve the accuracy of the submitted information, and prioritize and streamline event analysis. Few national surveillance systems [13,14] and other institutional safety reporting systems value the voluntary, anonymous, and confidential aspects of collecting information about adverse events and near misses. Some of these provide feedback in the form of monthly reports, case discussions and/or newsletters [15], rather recognizing the importance of educa-

tional interventions such as safety awareness and learning how to use the reporting system [16,12]. Such features are believed to result in great improvement for the reporting systems.

Objective

We describe an open-source Web application, Duke Surgery Patient Safety (DSPS), designed at our institution for the anonymous reporting of adverse and near-miss events as well as regular reporting to physicians and hospital administration. This program was designed to streamline this process in the Department of Surgery at our institution; nonetheless, it can be adapted to any patient care department. The primary goal was to design a program that would streamline adverse-event reporting with minimal time required by reporters in the ever-busy and high volume surgical environment. To the best of our knowledge, this is the first ever open-source program created to streamline the reporting of adverse events. More importantly, this program can be freely modified to sync with the existing reporting systems of institutions.

Implementation Goals

The primary goal of the DSPS application is to provide a mechanism for anonymous reporting of adverse events. In addition, DSPS should also automate repetitive tasks associated with the administration of patient safety initiatives, such as (1) send regular personalized reminders by e-mail to all potential reporters, (2) allow administrators to properly store, make changes, and reject individual reports as deemed necessary, and (3) generate automated periodic reports for individual practitioners and hospital administrators summarizing adverse report rates in a graphical format.

Design objectives

The overall objective of the DSPS project was to build a Web-based application that would allow for the anonymous reporting of adverse events. Before designing the application, we analyzed similar tools, including commercially available products, adverse event reporting systems from academic

institutions, and recommendations from the Institute of Medicine [17].

Our search resulted in a series of technical requirements that are highly desirable for the application:

- User interface should be simple and straightforward to enhance reporter participation

- The application should run on an Intranet to facilitate access by multiple computers within the same institution

- Reporters should have a minimum set of categories to classify their complications according to a standardized coding system determined by the institution, followed by a unique free-text description of the adverse or near-miss event (ANME) and its potential cause

- Reporters should be allowed to describe more than one ANME per patient without having to make a second patient entry

- Administrators should have the ability to change ANME that are inaccurate and reject others that are not considered to be adverse events

- Administrators should have the ability to check the ANME before it is accepted as a true event

- In order to incentivize reporting in the surgical setting, the application should remind reporters about its existence on a regular basis, also sending them reports about the numbers of complications submitted by their division

- Data extraction should be easy, allowing administrators to perform further analyses using external tools

The results from the search were implemented in the design of our application thus accomplishing the following design objectives:

- Simplifying the reporting process for frontline staff

- Eliminating multiple forms used to report adverse events

- Increasing the quantity and quality of occurrence data

- Improving response time by linking reports to department leadership and key personnel (clinical nurse specialist, unit educator)

- Improving evaluation and follow-up through a structured framework

- Enhancing the quality and safety of patient care and the employee work.

DSPS should ideally adhere to national data standards. Although ideal, achieving consensus on such standards remains a controversial matter. A recent effort by the National Surgical Quality Improvement Program [18] has attempted to classify some of the most common postoperative adverse events (Table 1). However, currently this classification is not comprehensive for most surgical sub-specialties and, therefore, we have attempted to design a method that will accomplish the following goals:

- Allow for data exchange across different surgical services and institutions

- Be flexible to ensure that specific needs of each surgical division are met

The software architecture was developed using a model similar to previous software applications from our group [19-21]. The programming language used was Java and the design model was Model-View-Controller (MVC) (Figure 1). MVC's three components are: a central Model, Views, and Controllers of the Model (Figure 2). The Views and the Controller are the application's interface. They represent the Model to the user. As for the central Model,

it displays the logic, as well as the database access, numeric algorithms, and algorithms for data manipulation. The Controller provides information to the Model while the View passes it from the Model to the users. Figure 3 is a diagram of the DSPS architecture.

Software interface

The Duke Surgery Patient Safety application provides interfaces for three classes of users: ANMEReporters, Administrators, and Report Receivers.

Table 1. List of adverse events as listed in the National Surgical Quality Improvement Program (NSQIP), 2005

Wound Occurrences
Superficial Incisional SSI
Deep Incisional SSI
Organ/Space SSI
Wound Disruption
Other (ICD-9)
Respiratory
Pneumonia
Unplanned Intubation
Pulmonary Embolism
On Ventilator > 48 hours
Other (ICD-9)
Urinary Tract Occurrences
Progressive Renal Insufficiency
Acute Renal Failure
Urinary Tract Infection
Other (ICD-9)
CNS Occurrences
Stroke/CVA
Coma >24 hours
Peripheral Nerve Injury
Other (ICD-9)
Cardiac Occurrences
Cardiac Arrest req. CPR
Myocardial Infarction
Other (ICD-9)
Other Occurrences
Bleeding > e units RBCs
Graft/Prosthesis/Flap Failure
DVT/Thrombophlebitis
Systemic Sepsis
SIRS
Sepsis
Septic Shock
Other (ICD-9)

Software architecture

Activity flow

Before the application was built, we evaluated the usual flow of activities for ANME reporting and how the application would be integrated into this system. This analysis resulted in the following flow of activities in the software architecture (Figure 4):

- Weekly e-mails are directly sent to health care professionals working with patients reminding them about the importance of ANME reporting and reminding them of the central Web site.

- When an ANME is identified, health care professionals go to the Web site and generate the report using a single reporting interface.

- Administrators receive an e-mail soon after a new ANME is reported. They access DSPTS and receive the information that will allow them to investigate the ANME in fur-

ther detail. This checking is performed through consultation of medical charts and administrative databases.

- Once the ANME is confirmed, the administrator returns to DSPTS and confirms its existence. Otherwise, the report can reject by the administrator.

- Confirmed ANME are included in a monthly report with information customized to individual practitioners and divisions.

ANME reporters

The interface for ANME reporters includes functionality that allows reporters to perform the following functions:

- Choose the surgical division, subspecialty, and primary surgeon and/or house staff associated with the ANME.

- Provide information that will allow for identification of the patient for whom the ANME is being reported.

- Select all pre-defined complication categories that are applicable to this patient, including a text description where reporters can add additional information as needed, including potential cause. Reporters also have the ability to delete complications prior to submission if a category is erroneously selected (Figure 5).

- Since at our institution the most frequent users of the system are surgical residents, the reporter interface also has a link to a repository of previous patient safety presentations. Usually residents prepare their presentations based on previous ones, and the inclusion of this additional resource ensures that they will frequently come to the DSPTS site, thus serving as a constant reminder of the importance of patient safety reporting.

Report receivers and administrators

The administrative interface was designed to allow the administrator complete control over all existing tasks (Figure 6). These include:

- Receive e-mail when ANME report is made

- Check reliability of ANME report and either accept or reject it

- Add new administrators. This function is of exclusive use of departmental adminis-

trators, so that they can delegate the function of divisional representatives. The administrator can also add new divisions and respective subspecialties, providers, reporters

- Add and modify new sets of complication categories that are specific to divisions
- Export ANME data in a spreadsheet so that it can be manipulated using data analysis software (e.g., text mining, statistical packages, neural networks, etc)
- Define report format and respective release dates for providers.

• Generate messages sent to all potential reporters (health care professionals working with patients) on a regular basis. These messages usually contain a message stating the importance of ANME reporting, also providing links to DSPS.

- Add educational files to an educational repository. These files function as a library aiding the resident who, at our institution, is in charge of the monthly patient safety case presentation.

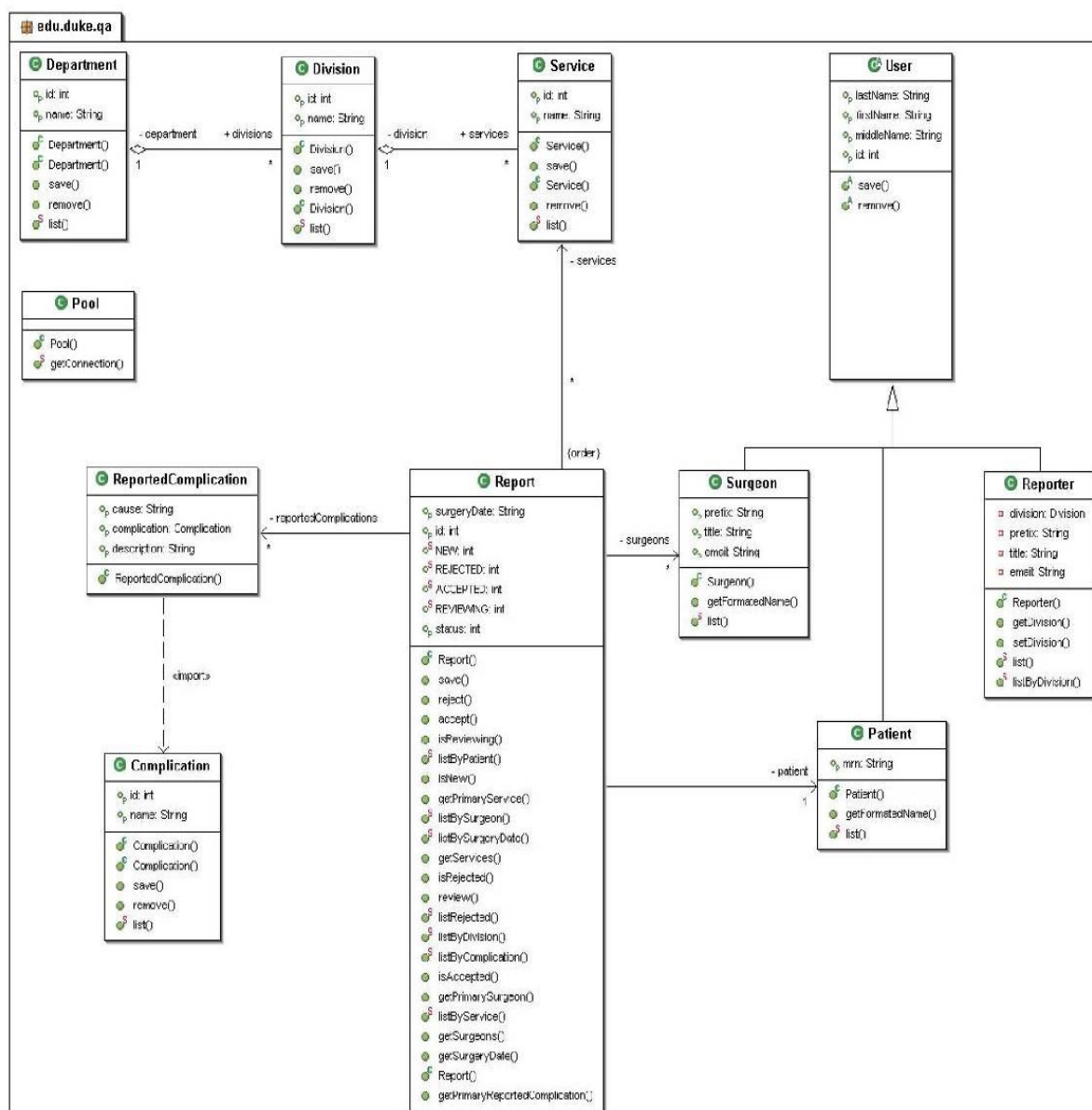


Figure 1. Model-View-Controller (MVC) as its design model.

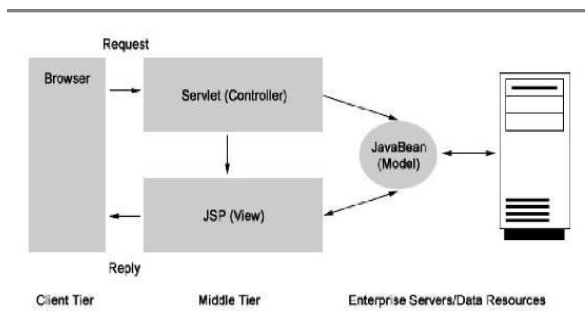


Figure 2. Controllers of the Model.

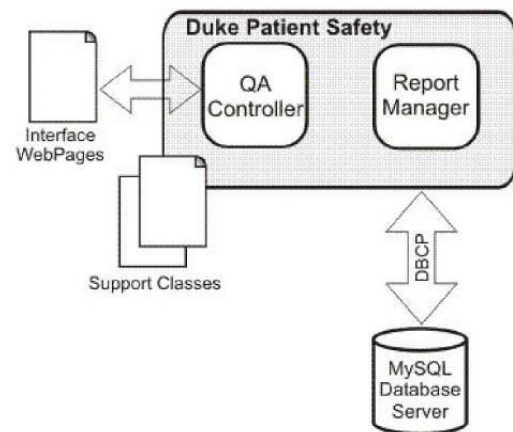


Figure 3. DSPS architecture.

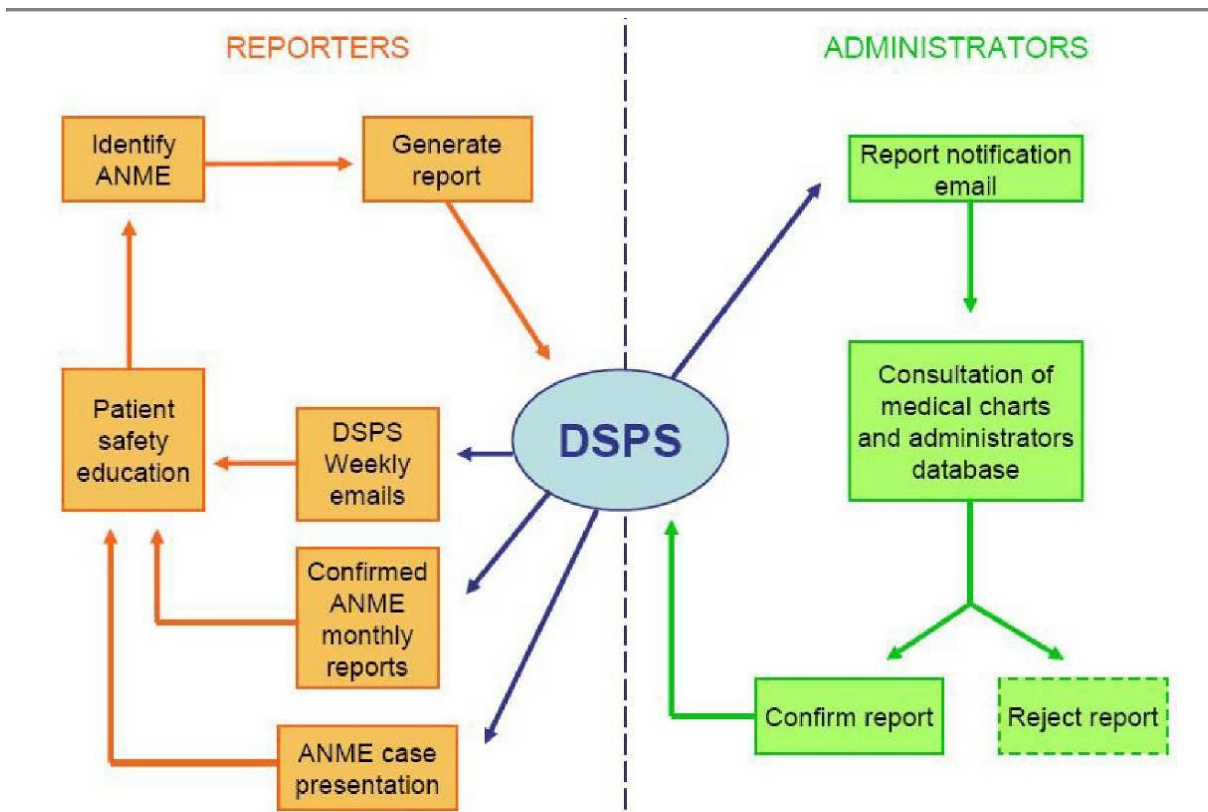


Figure 4. flow of activities in the software architecture.

Usability evaluation

Comprehensive usability tests were performed by formal usability analysis and a field observation period. Formal usability analysis was conducted in a manner similar to a previous study by the authors' institute [20] In short, twelve physician scientists (n = 10) and nurses (n = 2), from two institutions, were asked to participate to avoid bias from authors participating in the development of

the DSPS application. Six users tested the reporter's interface and the other six tested the administrator's interface. Each of these users, by self-report, rated as having average computer literacy with no previous experience with the DSPS application. Formal usability tests followed a protocol where users were observed by two evaluators (who were available to answer any questions from users) and had to complete assigned regulatory tasks.

The following DSPS application factors were evaluated: speed, easy of learning, easy of using, understanding of functionality, and navigation. The evaluators who observed the users made detailed notes about number of errors made while using the application. Each

participant was instructed to answer a questionnaire at the end of the formal usability analysis with items about interface problems, missing features, and suggestions for overall improvement.

Surgery information related to the adverse event:

Date: Please select below

November 2005						
S	M	T	W	T	F	S
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			

Please select all complications categories that apply to this patient, selecting one at a time:

Complication: Select complication from drop down list

Complications List:

Remove

Description:

Potential Cause:

Submit Report

For any questions or help on using this website, please contact Mariana McCready by:

Figure 5. Complication Report.

As with previous studies by these authors [20], field observations were conducted by one of the co-authors (MM) and consisted of observation of researchers and research administrators during the execution of common regulatory activities using DSPS. Meetings were held with investigators and research administrators in order to obtain detailed feedback concerning any concerns or suggestions for improvement, however we acknowledge that further studies with more users are needed for long-term testing.

Results Implementation

The current version of DSPS was designed to allow for the anonymous reporting of adverse events, their evaluation

and follow-up, while reducing the number of forms used and making the report-

ing process easier leading to an improvement in the quality and safety of patient care. Its current design incorporates the numerous suggestions received from formal and field usability tests. The DSPS application has been implemented in the Department of Surgery at Duke University Medical Center.

When making an anonymous report, the reporters are asked to enter the division/department name, surgeon and, if appropriate, subspecialty related to the adverse event by choosing from drop down boxes available. Then, they need to provide patient information such as MRN, last name, first name and middle initial. Next, reporters select the date of the complication in a calendar. All complication categories that apply to the specific patient are selected, selecting one

at a time from a drop down list. In sequence, reporters can add additional information about the adverse event descriptions and potential cause by typing into the appropriate text areas. At last, they mark the severity of complication based on Complications Grading System:

- Grade I - Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This

grade also includes wound infections opened at the bedside.

- Grade II - Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.

- Grade III - Requiring surgical, endoscopic or radiological intervention.

- Grade IV - Life-threatening complication (including CNS complications) requiring IC/ICU management.

- Grade V - Death of a patient.

The screenshot shows a web browser window titled "Duke Patient Safety :: Administration - Microsoft Internet Explorer". The address bar shows the URL: http://surgerysafety.duhs.duke.edu/servlet/QAController?command=administrators. The page content includes a navigation menu: Administrators » Surgeons » Reporters » Divisions » Subspecialty » Complications » Message » Report Message » OA Form » Quit. Below the menu is a table with columns: Surgery Date, MRN, Patient, Surgeon, Division, Subspecialty, Complication, and Qi submitted. The table is sorted by Surgery Date. The data rows are as follows:

Surgery Date	MRN	Patient	Surgeon	Division	Subspecialty	Complication	Qi submitted
E 2	2			Orthopaedic Surgery	Joint Replacement	death (intra or post-op)	false
E 2	2			Neurosurgery	Pediatrics	shunt infection	false
E 2	2			Neurosurgery	Pain-IT Therapy	wound dehiscence	false
E 2	2			Neurosurgery	Spine	post-op hematoma	false
E 2	2			Orthopaedic Surgery	Joint Replacement	other complication	false
E 2	2			Orthopaedic Surgery	Pediatric	wound infection	false
E 2	2			Orthopaedic Surgery	Spine	post-op hematoma	false
E 2	2			Neurosurgery	Not defined	shunt infection	false
E 2	2			Neurosurgery	Cerebrovascular	death (intra or post-op)	false
E 2	2			Orthopaedic Surgery	Sports Medicine and Shoulder	wound infection	false
E 2	2			Neurosurgery	Not defined	death (non-op)	false
E 2	2			Neurosurgery	Not defined	death (non-op)	false
E 2	2			Neurosurgery	Cerebrovascular	stroke	false
E 2	2			Neurosurgery	Not defined	death (intra or post-op)	false
E 2	2			Orthopaedic Surgery	Trauma	post-op hematoma	false
E 2	2			Neurosurgery	Not defined	shunt infection	false

Figure 5. Report Receivers and Administrators.

When the reporters are done, they must click on the "submit report" button. The department administrator will be notified immediately. Each administrator will check the consistency of reports made in their departments and either accept or reject them. Although the adverse event reports are screened by the administrator, one should be aware that researchers, physicians and national or-

ganizations interested in patient safety may have different goals.

Data standards

In DSPS, our approach has been to present surgical specialties with existing standards that are internal to each of the surgical departments using the application. Further modifications are made in the attempt to make the variables compliant with what ex-

ists in other divisions, ultimately allowing comparisons across subspecialties.

Usability

1. Formal usability

Results from formal usability testing are summarized in Table 2. Formal usability results demonstrated that, from the perspective of researchers, the DSPS application presented excellent speed (11/12 users strongly agreed), was easy to learn and use (10/12 users strongly agreed), had a functionality that was easily understandable (10/12 users strongly agreed), and a navigation that was intuitive (12/12 users strongly agreed). No users reported any problems in the questionnaire that was presented after formal usability testing.

2. Field usability

The first two months of field usability measurement were primarily focused on fixing software bugs, namely nonfunctional links to other Web pages and click buttons that did not work. DSPS users were encouraged during this time to submit their comments and suggestions directly to one of the co-authors (MM) who investigated any issues with the programmer (HM).

During this phase, one issue that was corrected was the automatic email that is sent on a weekly basis to all surgeons and reporters who use DSPS for reporting. Initially, it was not being received by the users on certain weeks.

Upon detection of the error, the programmers were able to readily correct the issue. Also during this phase, multiple users identified that the link they were receiving in the weekly automatic email was not working correctly. The users would click on the link and get an error message. However, upon reviewing this issue, it was an error attributable to the email system used at our institution, which frequently can not open links included in an email. To remedy this situation, additional instruction was included in the weekly email to copy and paste the link into a browser window.

Discussion

To our knowledge, this is the first description of an open-source application for reporting patient safety related events. DSPS provides a mechanism for anonymous reporting of adverse events and helps the administration of patient safety initiatives. At the time of this article, Duke Surgery Patient Safety has only been used within a few departments at Duke University, including the Department of Surgery; however, the free distribution of its source code under the GNU Public License is expected to spread its use among other departments and colleague institutions. Although this is possible, we have not tested the cross-application of our software yet, and therefore, we are unable to discuss possible difficulties that might arise. We recommend that potential users consult their institutional IT department for guidance in installation and customization.

There are many web-based reporting systems available, but most of them are restricted to one institution or they collect data on just one type of event such as medication errors and adverse events involving medical products. An example is a passive reporting system for adverse effects caused by vaccine. The events are voluntarily reported by the person who experiences them which leads to great underreporting, unconfirmed diagnoses and lack of temporal association [14].

Much of the difficulty with underreporting stems from the fact that many reporting systems focus blame on individuals rather than on the prevention of similar events. The importance of developing consciousness and awareness of patient safety, rather than generating individual blame, has the potential to greatly enhance the patient safety reporting system and the incentive to utilize the system. Ultimately, such system has the potential to improve patient morbidity and mortality in departments where administrative time is limited for members of the patient care team. We are confident that the simplicity and streamlined reporting of DSPS make it a valuable asset for our institution.

Table 2. Formal usability

DSPA speed is excellent.	Strongly disagree	0/12
	Disagree	0/12
	Neutral	0/12
	Agree	1/12
	Strongly agree	11/12
DSPA is extremely easy to learn	Strongly disagree	0/12
	Disagree	0/12
	Neutral	1/12
	Agree	1/12
	Strongly agree	10/12
DSPA is extremely easy to use	Strongly disagree	0/12
	Disagree	0/12
	Neutral	0/12
	Agree	4/12
	Strongly agree	8/12
It is very easy to understand all functionality available within DSPA (e.g., download files, upload files, etc)	Strongly disagree	0/12
	Disagree	0/12
	Neutral	1/12
	Agree	1/12
	Strongly agree	10/12
The navigation in DSPA is highly intuitive	Strongly disagree	0/12
	Disagree	0/12
	Neutral	0/12
	Agree	0/12
	Strongly agree	12/12

Conclusion Current utilization

DSPA is currently used by the Divisions of Orthopaedic Surgery, Neurosurgery, General Surgery, OHN (Otolaryngology, Head and Neck), Pediatric Surgery, Plastic Surgery, Urology and Cardiothoracic Surgery at Duke University Medical Center (DUMC). It is currently being expanded to other divisions within the Department of Surgery at DUMC, as well as other academic and non-academic centers.

Potential uses

Although DSPA was originally developed to fit the patient safety needs of the Department of Surgery at DUMC, its modification for use at other institutions is simple and can be easily accomplished by a few modifications in the open-source application. Several features are planned for future versions of DSPA. First, integration with administrative databases would enable our group to flag adverse events in a more automated manner. For example, if hypoglycemia is detected in an inpatient, this might indicate an adverse event (mismanagement of insulin treatment). Second, future versions should have the ability to obtain denominators (total number of cases) from administrative databases in order to generate ANME rates. These rates would

be more meaningful than simple frequencies. Implementations of both features require integration of administrative databases with heterogeneous architectures, therefore requiring an interface that may integrate well with XML standards as well as possibly legacy systems.

Potential reactions

According to the Committee on Data Standards for Patient Safety of the Institute of Medicine [22], three main reactions corresponding to the "cycle of fear" can occur once safety data are released. First, "kill the messenger" reactions are triggered and there is an attempt to shift the blame by questioning the measurement system and those conducting the evaluation. Second, "filter the data" starts as it is much easier to achieve better scores by 'gaming the system' than by actually changing and upgrading procedures. Third, "micromanage" response takes place. Reacting to immediate variation in the process data instead of conscientious investigation and remodeling will make the system less efficient. It is the hope of the authors that the release of patient safety reports through DSPA promotes the development of positive learning systems. Education attempts to change the shape of the performance distribution by

improving all parts of the process [23]. However, to accomplish this learning system phase, a self-reporting application such as DSPTS should not be an isolated solution. A crucial resolution is to give emphasis to safety itself rather than blaming. For example, we hope that ANME case discussions provide opportunity for improvement.

Availability and requirements

- Project name: Duke Surgery Patient Safety (DSPTS)

- Project home page: **Ошибка! Недопустимый объект гиперссылки.** (click link for Free software)

- Operating system(s): Linux/Windows
- Programming language: Java
- Other requirements: Java 1.3.1 or higher, Tomcat 5.x or higher

- License: GNU General Public License
- Any restrictions to use by non-academics: none

Abbreviations

- DSPTS-Duke Surgery Patient Safety
- ANME-Adverse and near-miss events
- DUMC-Duke University Medical Center

Competing interests

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

Authors' contributions

All authors have read and approved the final manuscript.

- RP - designed the application, assisted with software testing, conducted the usability tests, and wrote the first draft of the manuscript

- RL - assisted with the design of the application, reviewed the manuscript for intellectual content

- AS - assisted with the design of the application, reviewed the manuscript for intellectual content

- DOJ - assisted with the design of the application, reviewed the manuscript for intellectual content

- MH - assisted with the design of the application, reviewed the manuscript for intellectual content

- MM - assisted with the design of the application, assisted with field testing and software debugging, reviewed the manuscript for intellectual content

- HM - assisted with the design of the application, wrote and tested the source code for the application, reviewed the manuscript for intellectual content

- AM - assisted with the design of the application, assisted with field testing, reviewed the manuscript for intellectual content

- WR - assisted with the design of the application, assisted with field testing, reviewed the manuscript for intellectual content

Appendix

Programming language and development methodology

DSPTS was developed primarily using JAVA programming language, operating on a Tomcat server and having a MySQL database as its backend. We used a prototyping development methodology, starting with paper prototype and drawing requirements from that prototype. Once the requirements were reviewed, a first version was developed and tested. This cycle was repeated until the current version was obtained.

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Materials of conference

**INFLUENCE OF IODINE-DEFICIENCY ON
CLINICAL METABOLIC DISORDERS
FORMATION IN YOUNGSTERS**

Veremchuk L.V., Antonyuk M.V.

*Research and Development Establishment of Medical
Climatology and Rehabilitation – Vladivostok branch
of Far Eastern Scientific Center of Physiology and
Respiratory Pathology of RAMS Siberian Department,
Vladivostok, Russia*

Iodine deficiency as a pathological state is widely common in all population groups of Russia. The value of iodine for a human being is determined by the fact that this trace substance is an obligate structural constituent of thyroid hormones – thyroxin (T4) and triiodothyronine (T3). The iodine deficiency can lead to thyroid hormones production change, especially in the period of an increased demand for this microelement. The teenage is referred to this period.

The development mechanisms of the diseases conditioned by iodine deficiency are complex, many processes taking place in vivo are latent and, as a consequence, poorly known. A methodological approach of this research the investigation of correlation dependencies in the human body in iodine deficiency conditions in healthy young persons has become, that allows revealing the tendency of iodine deficiency pathology development in early stages.

226 youngsters aged 17-21 took part in the investigation, the iodine deficiency being diagnosed in 28% of them on the data of ioduria. Clinical anamnestic data, blood serum lipidic spectrum, hormonal and microelemental status, lipid peroxidation processes', cardiovascular fitness factors were used in the work. The findings were treated by variance analysis and multivariate statistics using the «STATISTICA 6.0» software package. For system and intersystem dependencies structure evaluation the pair and partial correlations of Pearson, which lined up into correlation pleiads with the help of P.V. Terentyev's grouping method, were used. As a rule, inside a pleiad (intrasystem) the relations are more determined (the correlation coefficient $r > 0,6$ at $p < 0,05$), the interpleiad (intersystem) relations are weaker ($r < 0,6$). Based on the weak correlation of interpleiad relations the coefficient $r < 0,6$, which formed the structural consistency of subgraphs taken for pleiads, was accepted as a threshold level.

As at the heart of the investigation the analysis of a body reaction at the iodine deficiency “disturbing” effect lied, the structural model was being built with respect to the “iodine content in urine” factor. The carried out analysis has let to reveal the intersystem relations of the first, second and third orders. For

the *first order* the direct action of iodine deficiency on the body's systems was taken. The *second order* of action testified to the mediation of the influence and the *third order* implied “distant” indirect intersystem dependencies.

As the investigation testified, a low iodine content in urine in youngsters influences (*the first order*) the cardiovascular system state and glutathione-peroxydase closely ($r=0,8$) associated with catalase (the system of lipid peroxidation). In this case the intersystem action of the *first order* is increased ($r=0,5; 0,4$), that testifies to the disturbing action of iodine deficiency. The intersystem dependencies of the *second order* are associated through LPO-AOD system (glutathione-peroxydase, catalase) with the lipid transport system and hormonal status. These relations are also strong enough ($r=0,5; 0,4; 0,6$), that testifies to tension retaining between the systems even in the mediated dependence. The indirect (*the third order*) intersystem relations, which enhance the iodine deficiency in youngsters on account of risk factors influence (smoking, heredity, metabolic processes disturbance) are also considerable in magnitude ($r=0,4-0,7$).

The intersystem (interpleiad) relations with the lack of iodine deficiency have demonstrated balanced mutual relations ($r=0,2-0,3$), creating system apartness (CVS, LPO-AOD, blood serum lipids, hormonal status), in normal state the iodine content in urine (*the first order*) affecting blood serum lipids and only indirectly influences the LPO-AOD and cardiovascular system.

Thus, at iodine deficiency in youngsters all the systems of the body interact strongly ($r=0,3-0,6$), at the lack of iodine deficiency the relations between the systems are weakened ($r=0,2-0,3$). At iodine deficiency in youngsters the primary target is the cardiovascular system, which disorganizes all the systems of the body through the LPO-AOD factors and hormonal status. Risk factors (cardiovascular system and metabolism diseases heredity, smoking) enhance this system disorganization. At the lack of iodine deficiency the thyroid hormones absorb iodine and then functionally affect the body through the lipid transport system.

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FEATURES OF AGE-SPECIFIC PHYSIOLOGY OF INHIBITORY-RELAXATION PROCESSES AND MECHANISMS OF BODY DEFENCE FROM EXTREME CONDITIONS OR FACTORS

Vysochin Yu.V., Denisenko Yu.P., Gordeyev Yu.V.

Saint-Petersburg State University,

Saint-Petersburg, Russia

Kama State Institute of Physical Culture,

Naberezhnye Chelny, Russia

The adaptive capability (adaptability) is the basis of life and individual development of biological systems. In its turn, the adaptability, as our research testified (Vysochin Yu.V. and others, 1983-2002), is in direct relationship to the capacity of inhibitory processes of the central nervous system, the capacity of inhibitory-relaxation functional system of urgent adaptation and defence (IRFSD) and the rate of voluntary relaxation (RVR) of skeletal muscles. It is the muscles' RVR emerging at the activation of the IRFSD against disorders in the ratio of the most important homeostatic constants (oxygen and hydrogen) *in vivo*, on account of which the practical realization of the protective function aimed, first of all, at the economical energy output, the efficiency upgrading and the rate of the body's energy resources compensation is carried out.

In different sets of experiments 320 school-children and qualified sportsmen (aged from 6 to 32) took part. As an adaptogenic factor a veloergometric exercise of maximal intensity was used.

At the analysis of the examination results it is established that, starting with the age of 6 and finishing with the age of 17, a progressive increase of the body weight (from $25,2 \pm 0,59$ kg to $70,1 \pm 0,68$ kg) and height (from $126,4 + 0,67$ cm to $178,8 \pm 0,75$ cm) occurs. From 17 to 29 years old the weight-height factors actually remain at the gained level.

The average capacity of the work on the veloergometer, as well as the weight-height factors, achieves its peak level by 17 years old increasing 4, 9 times as much compared to the age of 6, and further on doesn't undergo any substantial changes. But, if to analyse the relative capacity of the work (per 1 kilo of the body weight), another picture appears. The most progressive growth of the relative capacity is observed in those aged from 6 to 11 (increase by 54%). In the period from 11 to 16 it increases only by 7, 5%; from 16 to 17 – by 6, 2% more; and after 17 years old it remains almost at the same level gradually increasing by 2, 7% to 29 years old.

The relative rate of voluntary tension (RVTr) and maximal force (MFr) progressively increase from 6-year-old age and achieve their maximum to 18 years old. The RVTr and MFr total increment by this age makes 103% and 72% accordingly. From 18 to 28

years old the RVTr didn't change, and the force gradually increased by 19% more.

If the progressive increase of height-weight factors, contractile characteristics of muscles and physical efficiency are known well enough, then the new-onset age-dependent dynamics of inhibitory-relaxation processes and mechanisms of defence against extreme conditions or factors is unusual and absolutely doesn't fit in the social image of a growing body's individual development objective laws.

At the age of 6-11 already a very high muscles' RVR was registered. Then it gradually decreased and by 14 years old became minimal, having deteriorated by 22, 3%. After 14 the muscles' RVR started gradually increasing again up to the age of 29, and the early age (6-11) RVR level was achieved only by 20-25.

The age-dependent dynamics of the IRFSD was analogous. Then it progressively decreased (by 12, 6%) achieving its minimal values by 13-15 years old. After 14-15 years old the IRFSD capacity increased and by 23-25 years old took its peak level, and by 29 years old decreased a little.

It is worthy of note that the IRFSD level registered at the age of 6-8 years old was achieved by the age of 20-23 only.

In practice the dynamics of the IRFSD capacity was almost the very spit of the RVR dynamics and inhibitory systems' functional activity (IFA) of the CNS. The highest IFA level was also registered at the age of 6-7 already. Then the IFA progressively decreased (by 10, 0%) by 14 years old and again grew quickly up to 23 years old and remained at this very level up to 29 years old. The similarity of the dynamics and direct correlation dependencies between the IRFSD, IFA and RVR in all age periods, detected in this experiment, underlines the relevance of the CNS inhibitory systems with relaxation processes of the neuromuscular system and their direct participation in the formation of physiological defence mechanisms, the IRFSD in particular, of the body from extreme conditions or factors once again. The same character of these parameters' dynamics was observed in women as well, only their decrease at the age of 13-15 was less vividly expressed.

High levels of the IRFSD, IFA, RVR, the activity of inhibitory systems, nervous processes' balance, performance efficiency and other properties detected in 6-8-year-old children testify that at this very age already the child's body represents quite a formed (not anatomically, but functionally) living system, possessing all the necessary set of higher integrative, regulatory, adaptative and defence mechanisms to interact effectively both with positive hostility environmental factors, actively resist their stressogenic and damaging actions and struggle for survivability, reproductive property and longevity. It is no coincidence that, according to computations of biologists, the age

of human life must be not less than 150 years, and our great compatriot I.I. Mechnikov laid emphasis that a death earlier than 150 years old is not a natural, but a violent one.

Unfortunately, as our research have testified, after the age of 6-8 years old a progressive deterioration of all health criteria, achieving the maximum by 14-15 years old, begins. By this age the CNS affectivity increases essentially ($P < 0.001$); the functional activity of the inhibitory system and the CNS inhibitory control acutely deteriorate ($P < 0.001$); the IRSD and muscles' RVR capacity fall ($P < 0.001$) and a pronounced individual development hypertrophic type forms.

As a result, a healthy child's body with a quite completely formed mechanisms of adaptation and defence, prepared by the Nature for a long and happy life, for 7-8 school years loses its advantages, adaptive capabilities by 20-30% and becomes defenceless for any kind of harmful effects of the environment.

In this connection a considerable increase of a whole range of negative manifestations of the body life activity in school-children of middle and senior age, marked by many investigators, appears to be quite regular: the metabolism and energy resources consumption increase, the economical and operating efficiency of different organs and systems decreases, the CNS affectability increases and the cerebral cortex inhibitory control weakens, inadequate emotional reactions, neuroses and rapid fatigability emerge, adaptive capabilities of the body decrease, traumatism and case rate increase.

Regular sport activity, judging on the having been analyzed in our research dynamics of sport results growth and functional state of the body, breaks this endless vicious circle, promoting the restoration and perfection of one's own bodily machinery of urgent adaptation and defence. However, as our long-term experience and the experiments' results testify, usual sport activity does not suffice to solve this deep problem effectively. The development of a brand new complex system of special physical and functional training, the use of which from the early child age will provide the all-round development and perfection (training) of inhibitory-relaxation processes, one's own defence mechanisms and formation of the best rational types of long-term adaptation and individual development for an organism.

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CLINICO-EPIDEMIOLOGICAL ASPECTS OF CEREBROVASCULAR PATHOLOGY IN PRIMORYE TERRITORY

Gorelova I.S., Moldovanova V.O.,
Goulyayeva S. E., Goulyayev S. A.
*Vladivostok State Medical University,
Vladivostok, Russia*

By 2005 cerebrovascular diseases (CVD) had become making 21,2% in the blood system diseases structure in people living in Primorye Territory, having increased for seven years by 5,5%.

Their registration frequency in developed industrial cities (Artyom, Spassk, Lesozavodsk, Partizansk) reached 624,7/100000-1333,4/100000 people of the population, in rural area it was limited by 194,8/100000, that corresponds to the average statistical data of Russia.

The CVD incidence rate registration among adult population showed that among the hospitalized with the given pathology into the neurology unit of the City Clinical Hospital № 1, the patients with early manifestations of cerebrovascular insufficiency (EMCVI) make 2,2%; with insults (I) – 76,2%; with chronic CVD forms – 17,1%; with insults sequela (IS) – 4,5%. In the structure of cerebral accidents the ischemic one (II) prevails (66,9%) being ahead of the hemorrhagic insult (HI) by 49,2%. The transient ischemic attacks' (TIA) development level is ranging from 15,4%; the specific weight of subarachnoidal hemorrhages (SAH) makes 54,7% of the apopleptic shocks.

The seven-year long (2000-2006) dynamics of hospitalization of persons with the enumerated CVD forms is indicative of the reflecting them indexes' growth irregularity and of the maximal increase of such forms as II, SAH, TIA and chronic CVD forms by 2006.

Among the hospitalized persons with EMCVI men prevail; with insults, their sequela and chronic CVD forms – women do. The quotient of different insult forms development and chronic CVD forms frequency in men and women differ in the fact that TIA, II and chronic CVD forms (1,8, 1,14 and 2,17 times accordingly) progress in women more often than in men, and HI – 1,02 times as often in men than in women. The CVD development duration fall primarily on the age of 60-69 years old.

36% of the admitted to the hospital were sent by their Medical and Preventive Treatment Facility, 58,8% - Emergency Call Service, and only 5,2% came themselves. The MPTF sent primarily patients with EMCVI, chronic forms of CVD, IS, and ECS – with MCVI, HI and II.

Totally 804 persons died, 1,4% of them have fallen on the age category from 20 to 40; 6,9% - 40-49 years old; 17,9% - 50-59; 29,9% - 60-69; 43,9% - from 70 and older. There were 1,7 times more men than women among the died at the age of 40-49;

1,4 times – at the age of 50-59. After 60 years old there became more women: in the age category up to 70 their quantity exceeded the number of men 1,2 times, and after 70 – 2,3 times.

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SOME ASPECTS OF HEALTHY AND OBSTRUCTIVE PULMONARY DISEASE PATIENTS' RESPIRATORY SOUNDS COMPARATIVE ASSESSMENT

¹Guseinov A.A., ²Naumenko Zh.k., ³Kerimova A.M., ³Kichiyeva B.N., ³Kerimov K.Sh.
¹Dagestan State Medical Academy, Makhachkala,
²Scientific Research Institute of Pulmonology, Moscow, ³City Clinical Hospital, Makhachkala

Subject actuality

Modern computer technologies open up new possibilities in studying respiratory sounds acoustics, their treatment, archivation and standardization. Active research activity of scientists of a range of European countries is combined in the project CORSA (Computerized Respiratory Sound Analysis).

Russian scientists have developed an ingenious method of respiratory murmurs time and frequency characteristics analysis based on registration (scanning) of respiratory cycle – bronchophonography (BPG). The BPG is carried out with the help of computer diagnostic complex (CDC) “Pattern”. Such parameters as respiration period, instantaneous spectrum of respiration process within the limits from 200 to 12600 Hz, respiration acoustic mechanical equivalent (RAM) – the final integral characteristic representing the quantitative assessment of metabolic cost of the bronchopulmonary system for specific acoustical phenomenon activation and being expressed in millijoules (mJ), are investigated. The RAM measuring is performed in different frequency diapasons (RAM 0 – 200-1200 Hz - so called “basic” diapason, RAM 1 – 1200-12600 Hz - the whole spectrum, RAM 2 – 5000-12600 Hz – high frequency and RAM 3 – 1200-5000 Hz – low frequency ones), K – is the coefficient reflecting the same parameters in relative units in the corresponding frequency spectrums (K1 – the whole spectrum, K2 – high frequency and K3 – low frequency ones).

Purpose of work

Respiration patterns formation in healthy persons and obstructive pulmonary disease patients and their comparative assessment.

Materials and methods

We have examined 108 healthy persons (50 men and 58 women) and 166 (85 men and 81 women)

chronic obstructive pulmonary disease (COPD) patients: 91 bronchial allergy patients and 62 chronic obstructive bronchitis ones and 13 patients with these diseases' symptoms combination. All the patients had the functional disturbance of external respiration on the obstructive type in common. The BPG was carried out in the modes of quiet and forced respiration. More than 1000 of bronchophonograms have been analyzed as a whole. Nonparametric tests were used at the statistical treatment of the material. The statistical significance of difference between the factors in the examined groups was evaluated on the Mann-Whitney test.

Results

In the examined groups the authentic ($p < 0,05$) difference of RAM1, RAM3, K1, K3 factors in the mode of quiet respiration and RAM 0, RAM1, RAM2, RAM3, K1, K2, K3 ones at forced expiration was got.

Conclusions

Thus, we can hope that bronchophonography gives the possibility to get unbiased parameters of respiratory sounds which differ in healthy persons and obstructive disease patients, that can be used as a supplementary evaluative parameter in functional diagnostics of pulmonary diseases.

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INFLUENCE OF OXIDATIVE STRESS ON REDOX-STATE AND PERIPHERAL BLOOD HETEROPHILIC LEUKOCYTES APOPTOTIC PROGRAM REALIZATION

Zhavoronok T.V., Stepovaya Ye.A.,
Ryazantseva N.V., Petina G.V.,
Starikov Yu.V., Ageyeva T.S.

Siberian State Medical University of Federal Agency for Healthcare and Social Development, Tomsk, Russia

Purpose: oxidative processes and neutrophils apoptosis evaluation in acute period of community-acquired pneumonia (CAP).

Materials and methods: 34 patients with the verified diagnosis of CAP were examined, the control made 32 healthy donors. Neutrophils were released on the bi-gradient; the number of apoptotic cells and the intracellular level of oxygen active forms (OAF) were evaluated in cell cultures by the method of ductal laser cytometry; the number of oxygenized carbonyl-proteins (CP) and cytokine production (IL-8, FNO α) were defined by the IFA method; the OH group production, myeloperoxidase (MP), glutathione-peroxidase (GP), glutathione-reductase (GR), thioredoxine-reductase (TRR) activity, deoxidized (DG)

and oxidized (OG) forms of glutathione were investigated spectrophotometrically.

Results and consideration. During the acute CAP period the production of proinflammatory cytokines IL-8, FNO α and OH group by neutrophils into the incubation medium increased ($p < 0,05$) together with the activity increase of MP, which produced ClO $^-$ ions, that correlated with the pulmonary parenchyma inflammation intensity increase (the verification on the evidence of computerized tomography data). And with it the intracellular OAF amount in heterophilic leukocytes grew with protein oxidative modification (POM) processes promotion attended by the CP content increase and thiol-disulphide (TD) system balance shift towards oxygenized disulphide components formation. Against the OAF production increase in CAP patients the fact of total imbalance in glutathione-dependent neutrophil system has been registered, that was manifested in the GP activity inhibition, the decrease of DG amount and DG/OG integral factor characterizing the total TD potential capacity. The intracellular OG amounts' increase in neutrophils along with insufficient activity of GR and TRR reactivating reduction potential of the cell was registered. The HS/SS change is a repair moment in the processes of proteins oxidation and there can be no reparation in other OPM variants. Thus, the ratio of deoxidized thiol groups to oxidized ones and their ability to oxidative modification (buffer capacity) are important criteria of nonspecific cell resistance and enable their effective functioning. Antioxidative protection resources exhaustion and level increase of damaging functional proteins OAF leads to the creation of an oxidative stress situation in acute inflammation effector cells themselves. The redox potential decrease could promote the acceleration ($p < 0,05$) of lethal program of neutrophils' apoptosis, which is registered in the acute CAP period.

Conclusions. The intra- and extracellular prooxidants production increase, POM with CP accumulation, glutathione-dependent system activity decrease against the expressed DG/OG index fall and reduction potential regeneration system's inhibition in neutrophils are the signs of oxidative imbalance of effector cells of acute inflammation developing in CAP debut, that worsens the clinical course.

Intracellular redox- potential modulation can take part in the regulation of programmed cell death of neutrophils in OS conditions.

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EVALUATION OF NEUTROPHILIC AND ERYTHROCYTIC PROTEINS' OXIDATIVE MODIFICATION IN OXIDATIVE STRESS CONDITIONS

Zhavoronok T.V., Stepovaya Ye.A., Petina G.V., Starikov Yu.V., Ryazantseva N.V. Ageyeva T.S.
Siberian State Medical University of Federal Agency for Healthcare and Social Development,
Tomsk, Russia

Protein molecules are not only objects, but also participants of regulation processes of cells' oxidative metabolism, the imbalance of which is registered in case of oxidative stress (OS) formation.

The *purpose* is to detect the features of neutrophilic and erythrocytic proteins oxidative modification (POM) processes on the model of OS, which is formed in acute period of community-acquired pneumonia (CAP).

Materials and methods. 47 patients with the verified CAP diagnosis have been examined; the control group was made up of 32 healthy donors matching on age and sex. Neutrophils were released on the Ficoll-Paque density bi-gradient; plasma was collected; erythrocytes were washed out and hemolysate was prepared (1:10). The oxidized carbonyl group proteins were detected in neutrophils by the enzyme immunodetection method. In erythrocytes the proteins' carbonylation level, superoxide dismutase (SOD), catalase, glutathione peroxidase (GP) activity, deoxidized glutathione (DG) content were determined by spectrophotometric methods. The bitirosin formation and tryptophane oxygenation was evaluated in blood plasma by the fluorimetric method; the SOD, catalase activity, lipid peroxidation (LPO) products composition – diene (DC) and triene (TC) conjugates, malondealdehyde (MDA).

Results and considerations. In CAP patients in vivo the OS formation signs were registered. The LPO activation was attended by the increase of peroxide cascade toxicants in blood plasma: the DC, TC, MDA indexes were higher than the control ones ($p \leq 0,01$) against the background of catalase, SOD antioxidant enzymes' activity decrease ($p \leq 0,01$). The LPO products' excess lead to the mobilization and following degradation of antioxidants, creating their deficit in cells. The DG level in erythrocytes decreased at the GP, SOD, catalase activity combined inhibition against those in the control ($p \leq 0,05$), being indicative of these cells' reduction potential inhibition. In parallel, the restoration capabilities of disulfide cross-links, provoking the inhibition of a range of key SH-containing enzymes, turned out to be suppressed in red blood cells. The oxidative metabolism imbalance in the CAP debut promoted the activation of POM processes: the carbonylation increased ($p \leq 0,05$) both in acute inflammation effector cells (neutrophils) and in target cells (erythrocytes). Simultaneously the carbonylated proteins amount in plasma increased; the

proteins' oxidizability in vitro in conditions of incubation with the Fenton system components appearing to be increased: the carbonyl proteins increase was higher than in the group of control ($p \leq 0,05$). In the OS conditions at CAP the non-repair bitirozin cross-links and oxidized tryptophan – redox sensitive amino acids' oxidation products, accumulation in plasma was registered.

Conclusion

The accumulation of POM carbonyl products in plasma and blood cells, DG content and antioxidant enzymes decrease testifies to the expressed oxidative imbalance, developing in the CAP debut, in the system of functional proteins of the cell, that influences the pulmonary parenchyma state and worsens the disease course.

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UREA AND α -KETOGLUTARAT SPONTANEOUSLY FORM DEHYDROHYDANTOIN-5-PROPIONIC ACID IN VITRO

¹Kozlov V.A., ²Mat'kov K.G., ²Lyschikov A.N.

¹*Cheboksary state pedagogical university,*

²*Chuvash state university*

Cheboksary, Russia

By development of solutions for organs preservation we have found out, that solution EWS-1 (electrolyte water stabilization) does not prevent slices swelling in the test 24 hour incubations at +4°. Nevertheless, after addition 5mM α -ketoglutarat in EWS-1 and storages of this solution 24 hours at +4°C, it prevented a cortical kidney slices swelling authentically more effectively, than just prepared [1, 2]. Therefore we have assumed, any EWS-1 solution components enter a chemical reaction with formation of one or several derivatives possessing antiedematous action. The most probable candidates to us seem carbamide and α -ketoglutarat as carbamide falls into chaotropic compounds and it is inclined to formation ureid group. The ureid group, in particular, is present at all basic anticonvulsants of some derivatives of a hydantoin and in Karbamazepinum. All these compounds possess uniform property of chaotropic connections: to change physical and chemical properties of biological membranes, and to correct membranes permeability for Na^+ and K^+ . Besides hydantoin, possibly, prevent the brain swelling it previous development of the next epileptic attack.

Our experiments with the same medium, but for the lack of one of these compounds have appeared the indirect demonstration of what urea and α -ketoglutarat enter chemical reaction and form new compound. The solution containing both and urea and α -ketoglutarat prevented a cortical kidney slices swelling at a hypothermal incubation (24 h at +4° C) whereas in a solution without one of these two compounds slices have swelled. [1, 2]. Us were it is carried out the given research with the purpose of revealing of this hypothetical substance.

Materials, methods and research volume

Synthesis of required compound has been carried out in several ways:

1) urea (extra pure (EP)) and α -ketoglutarat (EP) (on 0,1 M of each compound) containing equimolar quantities the solution has been heat uped on a water bath up to 80°C with the subsequent cooling on air;

2) urea and α -ketoglutarat equimolar quantities were incubated 24 hours at ambient temperature;

3) urea and α -ketoglutarat equimolar quantities were incubated 24 hours at +4°C;

The synthesized bond has received working name KM-1. The synthesized compound chemical structure has been certain by a NMR 1H spectroscopy method. For this purpose crystals KM-1 have been received by means of spontaneous evaporation within 2-3 months. The NMR 1H spectrum has been registered on device Bruker DRX-500 with a working frequency 500,13 MHz as the dissolvent has been used DMSO – d6. The internal standard was GMDS.

The experience with kidneys slices hypothermal incubation. As mother substances are natural animal metabolites their not enzymatic or enzymatic interaction in vivo with formation studied is possible KM-1. For check of this assumption we have spent experience on a hypothermal incubation (+4°C, during 24 hour) rats kidney cortical slices in mediums EWS-1 and EWS-1b (Tab. 1). On 5 mm either α -ketoglutarat (EP), or L-arginin (EP), or an ornithine (EP) have been brought in these solutions. Besides the hypothermal incubation of sections in medium EWS-HT with a concentration gradient has been spent KM-1 (0,1; 0,5; 1,0; 2,0; 5,0; 10,0 mM). pH mediums measurement has been carried out by means of pH-meter Piccolo plus. In total for experiences of 20 white not purebred rats-mans have been used, it a kidney mass was 140-160 g. Rats contained on a vivarium standard ration. Rats have been subjected to an ethereal euthanizing before kidney withdrawal. Rats' decapsulate kidneys quickly have been cut on thin cross-section at ambient temperature. Up to 20 sections have been prepared from each kidney on the average. Immediately after a rifling all sections have been weighed on torsion balances and, besides after an incubation.

Table 1. Composition of incubating mediums, mM

To form a	EWS-1	EWS-1b	EWS-HT
NaCl (EP)	48,4	48,4	63,4
KCl (EP)	48,81	48,81	48,81
CaCl ₂ (EP)	2,25	2,25	2,25
KH ₂ PO ₄ (EP)	1,19	1,19	1,19
MgSO ₄ ·7H ₂ O (EP)	1,19	1,19	1,19
NaHCO ₃ (EP)	25,0	25,0	–
CH ₃ COONa (EP)	16,6	16,6	5,0
Mannitol (EP)	260,0	260,0	260,0
Carbamide (EP)	50,0	–	50,0
pH	7,85	7,85	8,4 (without KM-1)

Slices hydration research. Slices hydration have been research a gravimetry method on water loss at desiccation in a dry-heat case and expressed in dry tissue kg/kg.

Statistical analysis. The received digital stuff has been treated in Excel 2003 by descriptive statistics methods. As parameter of slices hydration distribution was close to normal the received digital material has been processed with t-test use. Data are presented in the $M \pm m$ form, where m – an average mistake. Authentic distinction was accepted at $p < 0,05$.

Results and their discussion

Synthesis during a urea colorless solution and α -ketoglutarat got a straw-coloured shade. Reaction proceeded both at heating, and at a room temperature, and at +4°C, reaction kinetic it was not researched by us. According to NMR 1H spectroscopy, the synthesized connection has been identified as 3(2,5 dioxo-3-imidazolin-4-silt) propionic acid (KM-1). It the gross formula $C_6H_6N_2O_4$, M.w.=170,116.

This substance of NMR 1H the spectrum is characterized by two multiplets presence of the methylene protons with chemical shifts 1,9 m.d. Both 2,25 m.d. And a singlet of an imide proton with $\delta=8,1$ m.d. Apparently, in water solution at pH=7,0 compound exists in the zwitterion form, and at acidifying a solution it can pass from lactam forms in lactim. On chemical structure the it compound by us meets dehydrogi-

dantoin-5-propionic acid. Relatives on structure compounds are hydantoin-5-propionic acid [3] and 4 (5)-imidazolon-5 (4) propionic acid [4], formed at the person, primates and rats during a histidine katabolism. Hydantoin-5-propionate – a termination products of a histidine exchange, it formed in an alternative path its katabolism from 4-imidazolon-5 propionic acids at FAD participation [3]. Theoretically, in vivo it can be transformed in dehydrogidantoin-5-propionate to dehydrogenation reactions with participation NAD^+ , $NADP^+$ or FAD. In view of that dehydrogenase reactions reversible, hydantoin-5-propionates synthesis from dehydrogidantoin-5-propionates is possible.

Proceeding from that synthesis of dehydrogidantoin-5-propionates can proceed in soft conditions (in vitro), it can be formed in some fabrics, both is spontaneous, and enzymatic, we have assumed. Mother compounds rather high concentrations are present at a liver and a kidney. In both bodies urea and α -ketoglutarat are synthesized (at deamination, glutamate transamination or in citric cycle). For check of our assumption of dehydrogidantoin-5-propionates endogenic synthesis we incubated rats kidney slices in initial medium where there was no urea, but there was α -ketoglutarat (Tab. 2). The bold font evolves the mediums which contain all substrates, ureas necessary for synthesis.

Table 2. Kidney slices hydration depending on presence or absence at medium of a urea combination or its precursors L-arginine and α -ketoglutarat, N=12, n=44 on the control and over each medium variant

Intact slices	2,97±0,04	
Slices incubated in medium: EWS-1	3,54±0,05	$p < 0,0001$ to intact slices
EWS-1b	3,55±0,03	$p < 0,0001$ to intact slices
EWS-1b + α -ketoglutarat	4,13±0,015	$p < 0,0001$ to intact slices & $p < 0,001$ to EWS-1 & EWS-1b
EWS-1 + α -ketoglutarat	3,11±0,05	$p < 0,0001$ to EWS-1 & EWS-1b
EWS-1b + arginin	3,48±0,085	$p < 0,0001$ to intact slices
EWS-1b + arginin and α -ketoglutarat	3,06±0,04	$p < 0,0001$ to EWS-1 & EWS-1
EWS-1b + ornitin	3,46±0,07	$p < 0,0001$ to intact slices
EWS-1b + ornitin and α -ketoglutarat	4,61±0,19	$p < 0,0001$ to intact slices & $p < 0,001$ to EWS-1 & EWS-1b

EWS-1 containing urea badly prevents a kidney slices swelling and after 24 h of an incubation at +4°C, 19 % a set of water, in comparison with intact sections of the same kidney are observed. In medium EWS-1b of a not containing urea the swelling size was similar. Addition in EWS-1b 5 mM α -ketoglutarat strengthens hydration more than in 2 times, this phenomenon the reason has not been researched by us. Nevertheless, 5 mM α -ketoglutarat by EWS-1 addition was a swelling prevented, statistical differences with intact sections were not observed, and in relation to EWS-1 and EWS-1b the swelling is authentic below. The urea precursor arginine 5 mM addition in EWS-1b does not cause any effect, the slices hydration is comparable to a swelling in EWS-1 and EWS-1b. But an arginine introduction together with α -ketoglutarat also effectively warns a swelling, as well as α -ketoglutarat introduction on EWS-1. To similarly arginine, the 5 mM ornithine does not influence a slices swelling size in EWS-1b. However 5 mM α -ketoglutarat addition does not a swelling preven-

tion, but moreover strengthens it which even is more, than only at one α -ketoglutarat presence in EWS-1. It is apparent, that effect absence is caused by in a kidney the ornithine cycle is reduced, unlike a liver. Ornithinecarbamoylase activity low (the ferment catalyzing citrulline formation from an ornithine and carbamoylphosphate) that is why an ornithine does not participate in urea synthesis. Whereas in a kidney arginase activity is high, it catalyzing hydrolytic arginine decomposition up to urea and an ornithine.

Thus, in urea absence case in incubating medium for endogenous synthesis, a condition urea synthesis case is reduces α -ketoglutarat dehydrating effect. In our opinion, it obliquely proves a dehydrodantoin-5-propionate synthesis opportunity from urea and α -ketoglutarat in a kidney cortical.

Studying has shown influences KM-1 on a kidney slices hydration parameters, that it compound prevents a slices swelling effectively and concentration-depending in parameters from 2,0 up to 10 mM (Tab. 3).

Table 3. A kidney slices hydration dependence on KM-1 concentration in medium EWS-HT, N=8, n=18 on the control and over each medium variant

Intact slices	2,67±0,02
EWS-HT without KM-1	3,07±0,05**
EWS-HT with KM-1 0,1 mM	3,03±0,05**
0,5 mM	3,04±0,06*
1,0 mM	3,01±0,05*
2,0 mM	2,82±0,03*
5,0 mM	2,74±0,05
10,0 mM	2,64±0,04

* p<0,01, ** p<0,001 to intact slices

Dehydrodantoin-5-propionate existence in alive objects the biological expediency can be explained by urea linkage necessity for inhibiting effect depression its high concentrations on cellular ferments. Presumably, dehydrodantoin-5-propionate can participate in maintenance pH cells, binding or giving protons by formation donnormoacceptor connections with the second nitrogen atom, or as an olefinic linkage tearing up result. For example, introduction 5 mM KM-1 on EWS-HT causes depression pH from 8,4 up to 6,9. Interreacting through a carboxyl with the lysine rest of amino group by protein, dehydrodantoin-5-propionate can chemically modify protein, varying its functional activity. Probably, dehydrodantoin-5-propionate somehow takes part in kidney cells protection and a liver against a swelling at a water balance change, for example, at drink. It directly follows from our experiments with kidney slices swelling prophylaxis. Carrying out of researches before a unknown metabolic path of formation dehydrodantoin-5-propionate in biological objects and an establishment of its physiological role is necessary

Conclusions

1. Urea and α -ketoglutarat are capable in a wide temperature range to dehydrodantoin-5-propionate spontaneous formation in vitro.

2. In without urea medium α -ketoglutarat is a kidney slice swelling causes. At urea presence or arginine its metabolic precursor α -ketoglutarat prevents a kidney slice swelling in the hypothermal incubation test.

3. Dehydrodantoin-5-propionate prevents a kidney in the hypothermal incubation test without dependence from urea presence.

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ULTRASOUND IMAGING DISTINGUISHES BETWEEN NORMAL AND WEAK MUSCLE

Koryak Yu. A.

*Department of Neurophysiology & Countermeasures,
State Scientific Center – Institute of Biomedical
Problems RAS, Moscow, RUSSIA*

Introduction

A number of studies have documented that the microgravity environment encountered during space-flight or simulated by using models of weightlessness induces alterations in skeletal muscle function [3, 10, 14]. In the absence of weight-bearing activity, strength loss is the most evident consequence of atrophy. Moreover, showed that muscle strength decreased during bed-rest or immersion and suggested that the loss of strength [11, 13] was due primary to muscle atrophy [4, 15]. Muscle atrophy has been shown to be pronounced in the lower limb muscles [17], and it has often been observed that the reduction of strength is greater than that of muscle size [17, 19]. Therefore, these observed changes following a period of immobilization may cause changes in fascicle length.

Most skeletal muscles in humans are more or less pennated [8], in which muscle fibres are arranged at an angle with respect to the line of action of the muscle. The angle of muscle fibres with respect to the tendon action line is an important functional characteristic of the muscle. A large pennation angle allows more contractile material to be placed along the tendon increasing the muscle's force generating capacity, results in a less efficient force transmission through the tendon and results in a reduced fibre length, compromising shortening velocity and excursion range [7]. Pennation angle changes proportionally as a function of isometric contraction intensity.

Muscle architecture, i.e. geometrical arrangement of fibres within a muscle, has been shown to have a substantial influence on the force-generating capabilities of the muscle [9]. This angulation (pennation angle) has been shown to affect force transmission from muscle fibres to tendon, and hence muscle force generation [8, 9]. The architecture of a skeletal muscle is an important determinant of its functional characteristics [8]. Human muscle architecture may be studied noninvasively *in vivo* both at rest and during muscle contraction, by using real-time ultrasonography [9]. Indeed, several investigators [5] have demonstrated that during isometric contractions muscle architecture undergoes remarkable changes. Changes in fiber length by contraction are thus expressed as fascicle length changes

In an attempt to improve our understanding of *in vivo* changes of muscle architecture, modern imaging techniques have been used [5, 9, 18]. Real-time ultrasonography enables *in vivo* muscle scanning and of-

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fers promise for a realistic determination of changes in muscle architecture [9]. Real-time ultrasonic (US) measurements were taken in the present study in the triceps surae (TS) muscle in healthy man and patients. In this report, we have studied by means of ultrasonography the relationships between architectural parameters [lengths fascicles (L), and pennation angles (Θ) of fascicles, and muscle thickness (H)] and level of force exerted in highly-subjects and patient with consequences of cerebral palsy. The purpose of our research work was to determine *in vivo* changes in pennation angle and fibre length in each muscle of the triceps surae complex [gastrocnemius medialis (GM), gastrocnemius lateralis (GL) and soleus (SOL)], both at rest and moment produced voluntarily during an isometric ankle plantarflexion. We employed real-time ultrasonography to visualize fascicles *in vivo*.

Methods

Subjects

Thirty subjects participated in this study. These subjects were assigned to two groups. The first group of subjects consisted of 8 healthy men (avg. age = 52 ± 3.6 years), and the second group of subjects was composed of 22 patients men and women (avg. age = 55 ± 3.4 years). Prior to the experiment, the details and possible risks of the protocols were explained to the subjects and written informed consent was obtained from each of them.

Ultrasound scanning

The longitudinal US images of the medial (MG) and lateral (LG) gastrocnemius muscles were obtained at 30% proximal level of lower leg (the distance between the lateral malleolus of the fibula and the lateral condyle of the tibia), and soleus (SOL) muscles were obtained at 50% of the distance between the popliteal crease and the center of the lateral malleolus using the B-mode ultrasound apparatus (Sonoline Elegra, Siemens, Germany). Briefly, the measurements were carried out while the subjects stood with their weight evenly distributed between both legs. The mediolateral widths of the MG and LG muscles were determined by ultrasound over the skin surface, and the position of one-half of the width was used as a measurement site. The echoes from interspaces of fascicles and from the superficial and deep aponeurosis were visualized [16].

A real-time B-mode US apparatus (Sonoline Elegra, Siemens, Germany) with a 7.5-MHz linear-array probe (with 80-mm scanning length) was used to obtain sagittal images of the GM, GL and SOL, at rest and at 50 % of plantarflexor MVC at the neutral ankle position. A transducer with a 7.5-MHz scanning head was placed perpendicular to the tissue interface. The scanning head was coated with water-soluble transmission gel, which provided acoustic contact without depressing the dermal sur-

face. The subcutaneous adipose tissue-muscle interface and the muscle-bone interface were identified from the ultrasonic image, and the distance from the adipose tissue-muscle interface to the muscle-bone interface was adopted as representative of muscle thickness. All measurements were performed on the right leg. During all measurements, subjects were instructed to relax their leg muscles. Each subject's right foot was firmly attached to a dynamometer (Cybex® II, USA). The subjects were verbally encouraged to perform static contractions with the ankle plantar-flexor with a maximum possible effort. Three contractions were performed by a 1 min rest interval between bouts and the highest value was considered the maximum voluntary contraction (MVC). US images were obtained during the experimental trial on the previously determined stronger leg. Each subject was then asked to maintain the stronger leg contractions for at least 2-3 s at the neutral ankle position.

The fascicle pennation angle (θ) was measured from the angles between the echo of the deep aponeurosis of each muscle and interspaces among the fascicles of that muscle [5, 9]. The length of fascicles across the deep and superficial aponeurosis was measured as a straight line between the insertion points of the fascicle, onto the aponeurosis of the muscle (1, 16). Muscle thickness (H) was measured as the distance between the superficial and the deep aponeuroses echoes, and L at rest was measured as the length of the line drawn along the echoes parallel to the fascicles from the deep up to the superficial [5]. US images were calculated by US-system, using program Magic View 300 (Siemens) with archiving the data by Sienet (Siemens, Germany). In each muscle the average of the five images was used for data analysis.

Statistical Methods

Standard procedures were used to calculate means and standard deviations (\pm SD). The statistical significance of the differences between the two groups of subjects were calculated by Student's t test for independent samples and between groups of subjects.

Results

The US findings in the patient groups were compared to of a control group. From the US image, it was observed that L and θ changed during in the passive condition and specially the active condition. The degree of L change was not identical for the three muscles. The effects relaxation and an isometric contraction of the triceps surae muscle (50 % MVC) on L were significant for MG and LG and there was also a significant interaction between control and patients in these muscles. In other words, in MG and LG, changes in L changes were larger with the SOL. In the active condition, L of MG were not different between control and patients, although in the passive condition the difference was significant. The L of SOL were not different.

From the US image, it was observed that and θ changed during an isometric contraction of the TS muscle. Changes in L , and were expressed as a function of relative torque. The θ change was not identical for the three muscles. The fascicle θ of MG demonstrated the greatest variation in three muscles. The effects of activation and relaxation positions were significant in all three muscles. The differences in MG fascicle θ because of changes in ankle positions were significant among control and patients both in the passive and active conditions. Fascicle θ of LG and SOL not differed among control and patient in the relaxation condition but not in the activation condition. For LG, and Sol fascicle θ were changes were larger in control with the patients. The mean values fascicle θ of MG, LG, and SOL an isometric contraction (50 % MVC) in the control groups increased by 60 %, 41 %, and 41 %, respectively; in the patient groups were a smaller increase, by 28 %, 26 %, and 36 %, respectively.

H of MG and LG were not significantly greater in control than in patients, but in SOL were loss than in control. Changes in H were expressed as a function of relative torque. H of MG at was no significantly different between rest and 50 % MVC. In contrast, H of LG and SOL increased from rest to MVC by 21.9 % ($p < 0.05$) and 17.9 % ($p < 0.05$), respectively. In MG and SOL patients was not significantly different either between different imaged. H LG and SOL were not significantly greater in patients by 10.7 % and 3.6 %, respectively, but MG was decreased by 3.6 %.

Discussion

Our results show that the US image method applied is valid and reliable for assessing the size of a large, individual, human locomotor muscle. This method can provide information on cross-section area changes along the entire muscle length in response to training, disuse or as a spaceflights.

Internal architecture of the TS complex (MG) was altered. Both fascicle length and pennation angle were reduced after in patients groups, this strongly suggests a loss of both in-series and in-parallel sarcomeres, respectively. This observation is in agreement with previous findings in disuse conditions [19]. The functional consequence of the decreased fascicle length was a reduced shortening during contraction. It is necessary to note, that at some patients with motor disorders, having restriction of mobility, the normal ultrasonic architecture of muscles was marked. It is possible to assume, that disuse of a muscle is not the unique factor influencing on the ultrasonic architecture of muscles. Studying of architecture of muscles at patients with various motor disorders allows to understand better the intimate processes in healthy persons under influence of various factors, including micro-gravitation, long space flights, where restriction of impellent activity takes place, despite of using preventive measures, and experiments on animals demon-

strate the development of a muscular atrophy in conditions of microgravitation.

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EFFECT OF ELECTRICAL STIMULATION OF LOW FREQUENCY ON ARCHITECTURE AND SOME CONTRACTILE CHARACTERISTICS IN MEN

Koryak Yu.A.

State Scientific Center — Institute of Biomedical Problems of the RAS, Moscow, Russia

Introduction

Gravitational loading appears to be necessary for the maintenance of human lower limb skeletal muscle size and force [Kubo et al., 2000; Shenkman et al., 2003; Koryak, 2001-2003]. Studies simulating microgravity have shown that exercise countermeasures can attenuate, but not completely prevent the loss of muscle mass and force [Koryak, 2000; Kawakami et al., 2001]. The muscle groups most affected by exposure to microgravity appear to be the antigravity extensors of the knee and ankle [Akima et al., 2001]. Among these, the plantarflexors seem to be the most affected [LeBlanc et al., 1998], likely due to their greater mechanical loading under normal gravitational conditions. Most notable after exposure to microgravity is a disproportionate loss of force as compared to that of muscle size [Kawakami et al., 2001], indicating that factors other than atrophy contribute to muscle weakness. The internal architecture of a muscle is an important determinant of its functional characteristics. There is a paucity of studies on the effects of disuse [Maganaris et al., 1998] or simulated microgravity [Kubo et al., 2000; Kawakami et al., 2000] on muscle architecture.

Purpose

The purpose of the present study was to investigate the internal architecture of the triceps surae [medial (GM) and lateral (LG) and soleus (SOL) muscles] in relation to the functional characteristics of the plantarflexors after 7-days of “dry” water immersion (DI) with exercise countermeasures [term-long low-frequency functional electrical stimulation (FES) trainings].

Methods

To simulate microgravity the DI model has been used [Shulzhenko, Vil-Villiams, 1976]. Six subjects (men-volunteers; 22.8 ± 0.8 yr, 1.84 ± 0.1 m, and 79.3 ± 4.2 kg) gave their written, informed consent to participate in this study, after the ethics committee of the SSC – Institute of Biomedical Problems of the RAS had approved the procedures involved. All the experimental procedures were performed in accordance with the Declaration of Helsinki. FES is applied to 4 muscle groups of both lower extremities. “Dry” electrodes (Ltd. «Axelgaard», USA) are placed on the skin above the quadriceps femoris muscles, the hamstrings, the tibialis anterior, the peroneal, and the triceps surae muscles. The synchronous stimulation of antagonistic muscle groups prevents unwanted joint movements. The FES-training is performed during 3 hours per day with 1 s «on» and 2 s «off» trains at intensity levels of 20-30 % of maximum tetanic force and a frequency of 25 Hz. The electrical stimulus was provided by the «STIMUL LF-1» stimulator (RUSSIA). The technical equipment consists of electrode trousers carrying stimulation electrodes for the 12-channels, and 2 interconnected 6-channel stimulators caned on a belt. Subjects performed a series of isometric plantarflexion contractions on an isokinetic dynamometer (Biodex, USA) at ankle angles of 0° (neutral ankle position: the foot plate of the dynamometer perpendicular to the longitudinal axis of the tibia). All measurements were carried out with the knee joint flexed at 90° . A real-time B-mode ultrasound apparatus (“SonoSite MicroMaxx”, USA) with a 7.5 MHz linear-array probe, and length of a scanning surface 60 mm and thickness of 10 mm was used to obtain sagittal images of the GM, GL and Sol at rest and at 50 % of plantarflexor MVC at the neutral ankle position. The fascicle pennation angle (θ) was measured from the angles between the echo of the deep aponeurosis of each muscle and interspaces among the fascicles of that muscle. The length of fascicles (L) across the deep and superficial aponeurosis was measured as a straight line (Abe et al., 2000). Shorter fascicle L fibres (ΔL_{muscle}) was determined as a delta between L and $\cos \theta$ fibres in the active comparison with the passive condition. All ultrasonic images were processed with use of the software package «Dr. ReallyVision» (Ltd. “Alliance – Holding”, RUSSIA).

Results

After the 7-day DI with application by FES-training, maximal plantar flexion torque increased on the average by 11.3 % (150 ± 17.3 vs 167 ± 6.7 H). After DI, in the passive condition, L fibres in the MG, and LG, and SOL has decreased for 12 % (from 32 ± 2

to 28 ± 1 mm), 13 % (from 36 ± 2 to 31 ± 2 mm), and 13 % (from 36 ± 3 to 32 ± 2 mm) but in the active condition by 18 % (from 26 ± 3 to 22 ± 2 mm), 22 % (from 36 ± 3 to 28 ± 2 mm), and 21 % (from 32 ± 2 to 26 ± 2 mm), respectively. The fascicle angles, in the passive condition, was decreased by 22, 20 and 16%; but in the active condition by 17, 22 and 17 %, respectively. Shorter fascicle lengths and steeper fascicle angles in the active compared with the passive condition show internal shortening of fascicles by contraction. Before DI ΔL_{muscle} the MG has found 7.9 mm after has decreased and has made 7.8 mm, and in Sol 5.9 vs 5.6 mm. Significant increased in ΔL_{muscle} from 0.9 to 3.3 mm were found by LG.

Discussion

After 7-days of DI a considerable increased of force, was observed in the exercise (+11 %) groups whereas absence of preventive actions results in reduction in MVC more than on 50 % [Grogor'eva, Kozlovskaya, 1987; Koryak, 2001—2006], and in Po more than on 30 % [Koryak, 1998, 2001, 2002, 2003]. Efficacy of FES-training for increased the contractile properties of skeletal muscles has been suggested in previous studies (Koryak, 1995; Mayr et al., 2000; Koryak et al., 2002). The insignificant increase in force of contraction in the present study can be assumed it is defined by slack intensity impulses. Internal architecture of the GM, LG, and Sol muscle was altered and this was only partially prevented by exercise countermeasures. Both fascicle length and pennation angle were reduced after DI with FES, this strongly suggests a loss of both in-series and in-parallel sarcomeres, respectively. The functional consequence of the decreased fascicle length was a reduced shortening during contraction. The loss of in-series sarcomeres would mean that this is likely to have implications both on the *force-length* and *force-velocity* relationships of the muscle. The observation of a smaller pennation angle during contraction after DI with FES will partially compensate for the loss of force, because of a more efficient force transmission to the tendon. The reduced initial resting θ probably, grows out reduction decreased tendon stiffness or of the muscle-tendon complex that finds confirmation in substantial growth ΔL_{muscle} of LG (with 0.9 up to 3.3 mm after DI) during contraction. This observation is consistent with the findings of Kubo et al. [2000]. In conclusion, FES-training was partially successful in mitigating the loss of function and architecture induced by prolonged DI. Apparently, by ascending during FES-trained a flow muscular afferentation (Gazenko et al., 1987).

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DISTRIBUTION OF DIFFERENT FIBRE TYPES IN NUMAN SKELETAL MUSCLE AND THEIR RELATION WITH NEUROMUSCULAR PERFORMANCE

Koryak Yu., Shenkman B.

State Scientific Center — Institute of Biomedical Problems of the RAS, Moscow, Russia

Introduction

The physiological, morphological, and biochemical responses of skeletal muscle have been extensively studied. Several recent studies have correlated different functional capacities of the intact human skeletal muscle, such as endurance, contraction velocity and strength, to the distribution of different fibre types in the muscle. A number of these studies have indicated that the tension per cross-sectional area unit is greater for the Type II (fast-twitch) fibers than for the Type I (slow-twitch) fibres. The purpose of this study was to compare twitch, tetanic, maximal voluntary contraction (MVC) with histochemically determined fibre type parameters in the triceps surae muscle group.

Methods

Sex subjects males volunteered for the study. Five the subjects were between the age of 20 and 30 years and one male was 38 years of age. The groups represented a variety of physical activity profiles, although none were considered extremely sedentary. The initial physical activity patterns for all subjects remained unchanged over the course of the investigation. The contractile properties of the triceps surae muscle group were measured using similar methods and procedures as described by Koryak (1995). The right leg was firmly clamped in a specially designed leg dynamometer in a standard position at a knee joint angle between the tibia and the sole of the foot 90° . The isometric twitch and tetanic contractions of the triceps surae muscle were induced by electrical stimulation of the tibial nerve supramaximal rectangular electrical pulses of 1 ms duration with a frequency of 150 Hz for the tetanic contractions [Koryak, 1995]. Stimulation of the tibial nerve was by a monopolar electrode. Twitch contractile measurements was included peak-twitch tension (P_t), time-to-peak tension (TPT), and half-relaxation time (1/2RT). Tetanic tension (P_o) were recorded during stimulation at 150 Hz at 30-40 V [Koryak, 1995]. The third test consisted of three MVC. The highest force of the three trials was recorded as the MVC. Within two day of the measurement of the contractile properties, needle muscle biopsies, using the technique described by Bergstrom (1962). The sample was taken from the belly of the right lateral gastrocnemius (LG) muscle. The samples were immediately frozen in cooled isopentane (using liquid N_2) and stored at $-80^\circ C$. Serial section, 10 μm in thickness, were cut from each sample using a cryostat maintained at $-20^\circ C$. The sections were stained for myo-ATPase after alkaline (pH 10.4) or acid (pH 4.3)

pre-incubation (Brooke, Kaiser, 1970). To classify the fibers as either Type I (ST) or Type II (FT), between 75 and 300 fibres were counted in each of the two myo-ATPase stained sections.

Results

Baseline data showed that the subjects had a significantly lower mean MVC ($485.6 \pm 38.3 N$) compared to P_o ($624.9 \pm 41.2 N$). Twitch tension (P_t), TPT, and 1/2RT agreed closely with values published previously (Vandervoot, McComas, 1986; Koryak, 1995). The histochemical parameters determined from the biopsy samples of the LG indication that the average distribution of ST fibres in the biopsy samples was $49.4 \pm 14.4 \%$ with a wide range of values from 30 to 91 %. Significant positive correlations were obtained for % ST and TPT ($r = 0.61$; $p < 0.05$), % ST and 1/2RT ($r = 0.81$; $p < 0.01$), and negative correlations were obtained for % ST and P_o ($r = -0.86$; $p < 0.01$). P_t and MVC forces did not show significant relationship with % ST fibres.

Conclusions

The absence of a relationship between contractions properties and fibre type distribution in some experiments may be attributed to use the voluntary contraction the features of which are an integral reflexion of both contractile properties of the muscles and the peculiarities of their CNS.

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GENERAL AND SPECIAL WORKING CAPACITY OF TRACK AND FIELD ATHLETES SPRINTERS AND STAYERS

Lazareva E.A., Rossoshanskaya N.S.,

Konovalova L.V., Gorlova L.A.

Ulyanovsk State University, Ulyanovsk, Russia

Physical working capacity is referred to the number of integral showings which are widely used for trackmen's potentiality estimation. There is a multitude of methods to define physical efficiency: based on maximum oxygen consumption measurement (MOC), PWC₁₇₀ test submission, lactic acid accumulation, anaerobic boundary, etc. The following questions arise fair-mindedly: Is only one and the same state evaluated by these methods? Are all the sides of physical efficiency diagnosed? Is it better to evaluate general or specific capability? How to define which defining method is the most suitable for physical condition evaluation?

As it is known, the work-out session in track and field is aimed at the development of either sprinter or stayer functional capabilities. In the previous work (Lazareva E.A., 2003) it was found that the defining of general physical efficiency with such a popular me-

thod as MOC measuring in the test of gradually increasing load shows the highest efficiency coefficients at stayers compared to sprinters. But can it say for a worse physical condition of sprinters (having the same category as stayers do)? The answer is negative because physical efficiency measurement of the same sportsmen in specific zones of relative potency shows that sprinters excel with maximal potency coefficients in the zone of anaerobic energy production; and stayers exercise maximal muscular power in the zone of aerobic and combined energy production, testifying that the caliber of both sprinters and stayers is defined by the predominant power supply source development degree and cannot be esteemed by general physical efficiency measurements. Really, if general physical efficiency (esteemed on the MOC showings) is defined by the final efficiency value, physical efficiency found out in the concrete zone of relative potency checks the development of the concrete bio-energy source and, therefore, bears more detailed information about the profile of energetic metabolism and allows detecting the predominant type of power supply. This confirms the idea that for effective trackmen's work-out session planning and physical efficiency diagnostics one should judge from the analysis of the results of a large number of tests. (Volkov N.I., 1989; Volkov N.I., Volkov A.N., 2004): gradually increasing load test for an integrated estimation of the maximum of aerobic and anaerobic capacities; critical power holding test for aerobic holding capacity estimation; single ultimate work test for glycolytic anaerobic power estimation; repeated ultimate work test for glycolytic anaerobic holding capacity estimation; ultimate anaerobic power test for anaerobic alactate capacity estimation; ultimate power reload test for alactate anaerobic holding capacity estimation. As a result of carrying out all these tests one can obtain an adequate valuation of physical fitness of a trackman – the physical fitness presupposing both general physical efficiency and all kinds of special working capacity data.

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HISTORY AND PROSPECTS OF SHAPE MEMORY ALLOYS APPLICATION IN SCIENCE, ENGINEERING AND MEDICINE

Muslov S.A., Styureva G.M.
Moscow State Medical Stomatological University,
Moscow, Russia

In latter days multifunctional predetermined-properties materials – the ones, which can change their properties under the effect of external factors and operation conditions (temperature, mechanical loading,

etc.), are finding more and more wider application in science, engineering and medicine. Certainly, the alloys with unique and most recently unknown physical and mechanical properties – thermomechanical shape memory effect (TME) and superelasticity (SE), refer to these materials. These alloys are able to reset unusually large inelastic deformations, show rubber-like behavior and damping properties, produce considerable stresses, etc., according to the predetermined program. It is generally recognized that the most vivid and the best representative of SE TME alloys is the intermetallic compound on the base of titanium nickelide NiTi – nitinol.

The application of shape memory super-elastic materials has allowed improving traditional properties and obtaining brand new functional ones of constructions having expanded their practical application areas radically. Non-detachable mechanical joints, drives, heat engines, fire alarms, various medical devices and instruments, vascular implants and filters, valves, occluders, bone implants, papillotomes, gallstone and urolith extractors, pulp extractors, hernioplasty meshes, etc., - these are a small part of these "intelligent" materials typical application examples.

During the last two-three decades in Russia and other technologically developed countries the shape memory alloys' application grows. On the results of a great number of investigations the international conferences ICOMAT, ESOMAT, EUROMAT, SMST, SMM, SMART, KUMICOM and others are held. A lot enough monographs and publications of fundamental and applied character testifying to considerable achievements in the sphere of titanium nickelide use appeared in the press. By now a great amount of patents on TME alloys, devices and products have been given. The most worked ideas and elaborations have reached the level of gross production, a definite part of products being made commercially. In spite of intent interest to these materials the information about the forecast application spheres of the last very often is incomplete or is contained in not easily accessible sources. The lack of special reference and bibliographical information on the given theme restricts the possibilities of scientific workers and engineers while solving concrete applied problems. The present paper informs about this gap compensation in terms of the patent base – one of the electronic library (EL) eSM@ divisions "Shape Memory Alloys Application In Science, Engineering And Medicine", creation. The base comprehends all the certificates of authorship and both native and foreign patents on the TME alloys from the date of their opening in 1960 up today. The resource has been registered in the Russian record of creation and utilization projects of the EL under the notion of "Information resources collection creation" and in electronic resources exchange scientific net.

The findings can serve a valuable educational and informative support for a community of specialists. The positive dynamics of the invention work results on the titanium nickelide application in medicine in Russia and abroad has been analyzed.

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INFECTIONS AND ALLERGY

Parakhonsky A.P.
Kuban medical university
Krasnodar, Russia

The immune response to antigenic stimulation represents the outcome of an integrated network of cells and mediators as well as of complex genetic-environmental interactions. Accordingly, it is quite reasonable to expect that immune responses to allergens and to bacterial, viral or parasitic antigens can influence each other.

The Th1/Th2 paradigm certainly represents an important reading key for a better understanding of the links between infections and allergy, where many bacterial and viral antigens preferentially induce a Th1-type response whereas parasites and allergens preferentially elicit a Th2-type response. However, explaining epidemiological data of associations between allergic and infectious diseases on the basis of the Th1/Th2 paradigm only is quite simplistic because of the many confounding factors influencing the final clinical status of subjects in epidemiological surveys. In fact, individual immune responses *in vivo* to allergens and infectious agents may vary also depending on the type and dose of antigenic stimulation as well as on the time and site of immune experiences.

While the relationships between parasitic infections and allergy are still controversial, a negative association between some bacterial or viral infections and allergic diseases has been reported by several studies. These negative associations as well as data emerging from studies of cohorts of allergic subjects (socioeconomic status, size and birth order effect) as well as from studies in population samples with different lifestyle provide support to the "hygiene hypothesis" (Strachan, 1989) suggesting that the reduced exposure to infectious agents during early infancy might represent a major factor for a prevalent Th2 polarization and the observed increasing prevalence of allergic diseases.

However, extensive evidence has been accumulated both in prospective and retrospective studies indicating, on the contrary, that some respiratory viral infections in childhood (e.g. RSV infections) are associated with a higher prevalence of allergy and asthma later in life, although it is not clear whether viral infec-

tions favour sensitisation or whether allergic subjects who experience respiratory viral infections develop asthma more frequently than non atopics. Certainly, rhinovirus infections have been proven to be a major cause of exacerbations of wheezing and of hyperresponsiveness of nasal and bronchial mucosa in both rhinitic and asthmatic patients. On the other hand, allergy can favour infections. In fact, ICAM-1 — a major receptor for human rhinovirus — is overexpressed in allergic inflammation, even in sub-clinical forms.

Our recent epidemiological study of exposure to food borne or orofecal microbes versus airborne viruses in relation to atopy and allergic asthma, might suggest a possible interpretation of the controversial issue whether infections favour or protect from allergy as well as of the inconsistencies impinging on the hygiene hypothesis. In fact, in our study food borne and orofecal exposure to microbes but not respiratory viral infections are associated with a lower prevalence of sensitisation and allergic diseases. Accordingly, the composition of the gut microflora or a high turnover of microbial products stimulating gastro-intestinal path, rather than infections diseases, might have a relevant role in protecting from atopy. Should this interpretation prove correct, mimicking a microbial education of the immune system might represent a new fascinating strategy to prevent allergic diseases and to revert the epidemic trend of atopy and allergic asthma.

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ROLE XANTHINEOXIDASE IN PATHOGENESIS OF THE GOUT AND ARTHRITISES

Parakhonsky A.P.
Kuban medical university
Krasnodar, Russia

Gout is a disease barely investigated at the present time. We know its cause, uric acid, we know the enzyme that converts purines to uric acid, xanthineoxidase, and we have an inhibitor, allopurinol, which acts as an effective preventative agent. However, there are a series of unanswered questions outstanding. The first is why is the relationship between the plasma uric acid and the development of gout so poor? For instance, in chronic renal failure uric acid levels are very significantly elevated, but gout a relatively uncommon problem. Secondly, why is gout a joint disease and why does uric acid not precipitate everywhere else? The solubility of uric acid in synovial fluid is no greater than that of plasma. Perhaps the clearance of uric acid from the joint is the problem, but there are other membrane systems where one

might imagine there could be difficulties, but no difficulties arise. Most patients with ischaemic limbs with a degree of renal failure experience no problems. An hypothesis is that the joint itself contributes to urate production making it an environment where super saturation can occur if plasma levels are elevated. If such a mechanism existed, the most likely explanation would be that the enzyme, xanthineoxidase, was up regulated somehow within the synovial membrane.

Our understanding of this enzyme has changed dramatically in the past few years. Firstly, it is now known that the conversion of purines to uric acid is only one of the functions of this redox centres enzyme. There are two other redox centres in the enzyme, one site, which is known to reduce oxygen to superoxide and a other site - an iron sulphur centre whose function is less clear. Recent studies have shown that the enzyme can serially reduce nitrates to nitrites, nitrites to nitric oxide and nitric oxide reacts with superoxide very rapidly to produce peroxyxynitrite. Nitric oxide, superoxide and peroxyxynitrite are powerful anti-bacterial systems. This raises the question - does the joint have a powerful anti-bacterial system and is the development of gout a reflection of this process?

Our interest in this area was stimulated when we took note of the fact that the levels of xanthineoxidase were very high in breast milk of lactating mammals (Stevens C.R. et al., 2000). A series of studies have now clearly demonstrated that the function of this enzyme is antibacterial and its purpose to protect the neonatal stomach and perhaps the lactating breast.

Now we shall consider infective and reactive arthropathies. Isolating intact organisms from the joint of patients with a bacteriamia and septicaemia is very difficult and indeed, most bacteraemic and septicaemic illnesses are not associated with an infective arthritis. The synovial membrane - is a fragile structure with multiple vessels for the most part supported by fatty tissue, potentially easily traumatised and able to leak. This structure is necessary for the correct physiological function of the joint allowing cartilage, which is avascular, but metabolic active. It is therefore at risk, and the presence of an antibacterial system, especially for the joint, would minimise this.

The evidence is recently found that the synovial micro vessels have an enhanced capacity to generate reactive nitrogen species and preliminary evidence that isolated synovial endothelial cells have an enhanced capacity prepared with other micro vessels to produce xanthineoxidase. It allows to connect these observations, and suitable experiments to do conclusion. In this presentation, we use teleological centred arguments to develop this hypothesis utilizing examples from other species in the animal kingdom.

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DEVELOPMENT FEATURES OF DISCIRCULATORY ENCEPHALOPATHY IN PERSONS SUBJECTED TO IONIZING RADIATION

Podsonnaya I.V., Shumakher G.I.
Altai State Medical University, Regional Wars Veterans Hospital, Barnaul, Russia

Epidemiological surveys showed that in accident consequences liquidators (ACL) in Chernobyl Nuclear Power Plant vascular damages of the central nervous system take one of leading places in disease incidence structure being the main reason of disability, social maladjustment and mortality.

The investigation purpose is to study the features of chronic brain ischemia in persons subjected to radiation effect.

Materials and methods

An examination of 536 men aged from 39 to 60 years old having taken part in Chernobyl disaster clean-up in the period from 1986 to 1988 (the first group) was carried out. 436 men with burdened radiation induced anamnesis made the control group (CG). Both groups were representative in age, physical comorbidity, intensity of encephalitic semiotics for April, 1986. The patients' state evaluation was carried out on one diagnostic algorithm taking into account physical and neurologic state, radiological anamnesis, laboratory-instrumental investigation methods including brain CT, MRT.

The statistical treatment of the material was carried out with the help of the Biostat program. The Student's criteria were used for pair values; the differences were considered to be authentic at $p < 0,05$.

Research results

For the accident moment there were no cerebrovascular insufficiency signs registered in the ACL, in 20 persons (4,2%) of the CG there was semiotics of initial signs of cerebrovascular insufficiency (ISCI) observed. A year after the emergency works the clinical picture of cerebral circulation insufficiency became apparent in 108 liquidators, that is 2,2 times as more than in the CG patients (49 persons). Among them the ISCI in the ACL made 9,9% (53 persons), in CG patients - 5,6% (27 persons); clinical implications of dicirculatory encephalopathy (DE) were detected in 10,2% of the ACL and 4,5% of the CG patients accordingly. In the ACL the organic manifestations of encephalitic pathology were represented by the I stage DE (8,9% of the cases) and the II stage DE (1,3% of the cases); in persons having been subjected to the radiation effect - only DE of the I stage (4,5%). For the following 3 years the DE was formed in 16,0% of the ACL: I stage DE - in 9,7% (52 persons), II stage DE - in 6,3% (34 persons); in every third liquidator (35,4%) the ISCI was registered. In patients without radiological anamnesis the DE was detected in 15,6% of the cases (75 persons): I stage DE - in 14,2%, II

stage DE – in 1,4%), and the ISCI increase for three years made in them 15,8%.

The five-year-postaccident-period was characterized by the ISCI predominance (2,8 times as much; $p<0,01$) over the DE frequency both in the ACL (51,9% and 18,7% accordingly) and in the CG patients (ISCI – 37,9% of the cases; DE – 20,6% of the cases) with relatively stable state of cerebral hemodynamics. During the following 5 years (up to 1996) in the ACL the steady progredient course of chronic brain ischemia was registered. Clinical DE manifestations are detected in the majority (84,1%) of the liquidators (I

stage DE – in 41,8%, II stage DE – in 37,5%, III stage DE – in 4,8%). Relatively healthy, i.e. having no clinical manifestations of chronic brain ischemia, 5,2% of the ACL (28 persons) remained. Among “unirradiated” persons the DE development dynamics was less expressed. In this group the ISCI (42,5%) and I stage DE (36,6%) patients prevailed.

The key moment of the 100% DE development in the ACL is a 15-year period after the effect of small radiation doses (Table 1).

Table 1. Discircular encephalopathy development dynamics in the examined patients for the period of 15, 20 years after the accident

Diseases	1 group (ACL), n=536				2 group (control), n=480			
	2001		2006		2001		2006	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%
ISCI	0	0	0	0		36,2	71	14,8
I stage DE	138	25,7	1	0,2	196	40,8	201	41,9
II stage DE	350	65,3	444	82,8	78	16,3	169	35,2
III stage DE	48	9,0	91	17,0	12	2,5	32	6,7
Total DE patients	536	100	536	100	286	59,6	402	83,8

By that time the clinical picture of cerebral discirculation in 65,3% of the cases (350 persons) had been in accord with II stage, in 25,7% of the cases (138 persons) – the I stage, in 9,0% of the cases (48 persons) – III stage. The DE development dynamics in the CG persons bore a more gradual, progressive character, making 59,6% (286 persons) with the prevalence of I and II DE stages (40,8% and 16,3% accordingly). The cerebral affection manifestations corresponding to III DE stage were registered only in 12 patients (2,5%), that is 4 times less than in the ACL ($p<0,001$).

By 2006 (20 years after the accident) the diffuse ischemic cerebral affection clinical picture had been represented by II stage DE in 82,8% ACL, III stage DE – in 17,0%. In most of them there were cognitive disorders of various manifestation degree, which were combined with local neurologic syndromes (discoordinatory 88,6%, pyramidic 77,4%, psychoorganic 71,6%, progressive vegetative insufficiency 96,1%). The development of psychoorganic syndrome of different manifestation degree was registered in 76 participants of the emergency works (14,2%) by 1996, by 2006 their number grew 5,1 times as more (384 persons; $p<0,001$). In persons of general population these factors were significantly lower – 0,4% and 4,6% accordingly ($p<0,001$), that again confirms a more favourable type of the DE course in persons without radiation anamnesis. The increased brain epiactivity development has become specific for DE in persons with radiation anamnesis. In 1996 14 such patients (2,6%) were found out, by 2006 their number had increased up to 69 (12,9%;

$p<0,001$). In the CG patients there were no epileptic phenomena registered.

Among the examined second group patients by 2006 the DE had been registered in 83,8% of the persons, almost the half of the patients (41,9%; 201 persons) having I stage DE, 35,2% (169 persons) – II stage DE, that is 2,8 times less than in the ACL. III stage DE was detected in 32 patients (6,7%); 7 patients (1,5%) were relatively healthy, i.e. had no clinical signs of DE.

Thus, the results of 20-year long observation showed that in persons subjected to ionizing radiation the development of chronic cerebral ischemia is characterized by an early and more “malignant” type of course compared to the patients of general population, for whom a gradual onset rate and a less expressed brain affection are definitive.

Conclusions

1. Persons subjected to low-intensity ionizing radiation are referred to the high risk group of chronic cerebral ischemia development.

2. In liquidators of Chernobyl Nuclear Power Plant breakdown aftereffects the development of chronic cerebral ischemia is characterized by an early and more “malignant” type of course compared to the patients of general population.

3. The discirculatory encephalopathy course in accident consequences liquidators in Chernobyl Nuclear Power Plant bears gradual character: from stormy augmenting of cerebral affection symptoms during the first two years after the radiation, relative stability of the disease clinical implications in the following 5-6 years and then intensively – as a progressive diffuse

process of encephalitic failure with forwardness of vegetative dysfunction, psychoorganic syndrome and epilepsy.

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INFRINGEMENTS OF HOMEOSTASIS OF LIPID AT PATIENTS WITH CHRONIC PYELONEPHRITIS

Rudichenko E.V., Novgorodtseva T.P., Antonjuk M.V.

The Vladivostok branch of the Far East centre of science of physiology and pathology of breath Siberian branch of Russian Academy of Medical Science - scientific research institute medical climatology and rehabilitation, Vladivostok, Russia

Wide prevalence of chronic pyelonephritis, variability of current, the adverse forecast - all this causes necessity of early diagnostics and perfection of methods of treatment of this pathology. During recovery regress of clinical symptoms of disease outstrips normalization of metabolic infringements. Than more hardly and longly illness, backlog of metabolic remission from clinical is especially expressed. Among metabolic infringements which are one of the reasons of progressing chronic pyelonephritis, the role lipids and a condition of lipids peroxidation is widely discussed. Change of a functional condition antioxidant system and excessive activation of processes of lipids peroxidation creates the certain conditions for structural reorganization of lipids components of cellular membranes. Revealing probable variants of metabolic infringements is actual at chronic pyelonephritis, development pathogenesis the proved address methods of the regenerative therapy directed on metabolic correction.

The purpose of research – to study features of lipids homeostasis, processes of lipoperoxidation at patients with a chronic pyelonephritis in a phase of remission and a latent inflammation.

226 patients chronic pyelonephritis in a phase of remission (73,4 %) and in a phase of a latent inflammation (26,5 %) in the age of 48,9±0,8 years are surveyed. Among surveyed women (69,9 %) are prevailed. At 46,9 % secondary chronic pyelonephritis proceeded on a background nephrolytiasis. In research did not include patients with chronic renal failure and arteriosclerotic heart disease.

Research a spectrum of lipids of whey of blood and redistribution of structure phospholipids (PL) in red blood cells is lead. A condition of system of antioxidant protection (AOP) judged on an integrated parameter of antioxidant activity (AOA) of plasma of blood. An intensification of processes the lipids perox-

idations estimated in red blood cells on increase malonic dialdehyde (MDA).

The analysis of structure of serum lipids in 53 % of cases has revealed its infringement. Distribution on types according to classification of Frederickson has shown, that for patients chronic pyelonephritis characteristic is dislipidemia IIa type. Redistribution of structure of phospholipids of red blood cells and fat acids (PA) included in them is established. The orientation of changes is expressed by decrease in a share of phosphatidilholine (PH) and sphingomieline (SM), increase phosphatidiletanolamine (PE) and phosphatidilserine (PS). The estimation of a condition of system the lipids peroxidation - AOS at 67,6 % surveyed has shown oppression of processes of lipoperoxidation. At 11,9 % of patients processes the lipids peroxidation were at a physiological level. The condition of hyperoxidation, expressing in increased level of MDA in blood has been revealed in 22,6 % of cases. The high factor MDA/AOA has testified about insufficiency of system AOS. Such condition of system the lipids peroxidations - AOS creates conditions for an aggravation of disease.

With the help of methods of the multivariate statistical analysis (factorial, cluster) three are allocated most frequently meeting clinic-metabolic a variant of metabolic infringements distinguished by character.

The first variant is characteristic for patients chronic pyelonephritis in a phase of remission and a latent inflammation with duration of disease till 5 years, rare aggravations (no more than 1 time one year), in whey of blood reveal the increased level of cholesterol of very low density lipoprotein (VLDL), in red blood cells - shares PS, total contents $\omega 3$, $\omega 6$ FA, a high level of nonsaturation, oppression of processes peroxidation on a background of high activity AOS.

The second variant meets at patients with chronic pyelonephritis in a phase of a latent inflammation the anamnesis of disease of 8 years, frequency of aggravations up to 2 times one year, in whey – hypercholesterolemia the easy degree, increased level VLDL, cholesterol of low density lipoprotein (LDL), are broken viscously - elastic properties of a membrane or red blood cells, ratio PH/PE caused by change, level MDA and parameter AOA are reduced.

The third variant is observed at patients chronic pyelonephritis in a phase of remission and a latent inflammation with duration of illness more than 8 years, frequency of aggravations up to 3 times one year is characteristic easy hypercholesterolemia, increased level of VLDL, LDL, deep metabolic changes of components of lipids of a cellular membrane - disbalanced structure FL and included in them $\omega 3$, $\omega 6$ FA on a background of the debalanced processes the lipids peroxidations - AOS.

The received results have clinical value for forecasting current chronic pyelonephritis and a choice of adequate methods of secondary preventive main-

tenance of disease. At carrying out of medical rehabilitation the differentiated therapy directed on correction of realization of metabolic infringements is expedient.

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EXAMINATION AND TREATMENT OF PATIENTS WITH HEMORRHAGE COMPLICATED GASTRO-DUODENAL ZONE PEPTIC ULCER DISEASE

Chernov V.N., Maslov A.I., Barokov E.M.
General Surgery Department of Rostov State Medical University, Rostov-on-Don, Russia

At the General Surgery Department of the RSMU and in the emergency hospital №2 of Rostov-on-Don during 1996-2007 163 patients with hemorrhage complicated gastro-duodenal zone acute ulcers had been observed. The cause of acute ulcers appearance in 40 patients were stressing situations, in 69 – primary trophic disturbances, in 18 – burn disease, in 36 – chemical agents (medicaments, alcohol). All the patients were hospitalized to the surgical hospital with bleeding in emergency order. 28 (11,1%) patients needed surgery (the retroclulsion was performed in 16 cases of them). Two patients died of a heavy blood loss at the admission in the admitting office (late hospitalization). In the rest 133 (81,5%) patients the bleeding was stopped nonsurgically (endoscopy, medicaments).

At the admission the patients were prescribed the infusive, sedative, hemostatic, antacid and anti-ulcer therapy. An important role was played by the transfusion of blood components and substitutes.

After bleeding control together with generally accepted clinico-laboratory studies the instrumental examinations were performed in accord with the methods developed at the Department:

- endoscopic examination with the obligatory study of the esophageal junction and big duodenal nipple (BDN).
- multiplanar X-ray examination;
- study of the acid-forming function of the stomach with the help of computer pH-metria;
- stomach motor function study;
- Helicobacter pylori detection.

The findings testified that an X-ray examination against the continuing bleeding is inefficient. We carried out this study on the 3d day after bleeding control.

The gaster acid-forming function study data let us give up on the existing before the present day notion: hiper-, hipo-, and normal acidity. Only on the in-

dication of acidity production, alkalizing function and vagus reaction on blockers we got 8 patient groups, only 3 of which needed a further surgeon observation with a view to a possible surgery.

The vegetative nervous system (VNS) investigation has allowed evaluating the state of the sympathetic nervous system, which promotes the stomach and duodenum mucous coat protective functions enhancement (myxopoiesis, carbonates development, etc.). On the state of hypothalamic centers of the VNS and peripheral terminals we have marked out 9 functional patient groups, which were also distributed according to the problem of treatment and prognosis.

The endoscopic studies let not only determine the ulcer focalization, sizes and state, but detect the hiatal hernia (HH) presence, the BDN state, malignant transformations suspect zones, etc. I.e. it allows detecting the pathology, on which to a large extent the choice of surgical tactics depends. So, for example, with the HH presence one doesn't have to expect the intended result from a stomach and duodenum operation without the esophageal hiatus correction.

An important role in the gastro-duodenal zone ulcer therapeutic approach determination is played by the stomach motor function. So, at dismotility and other causes (BDN pathology) it is not possible to restore the physiological food passage and, therefore, it is impossible expect a demandable effect from the gastric resection.

The detection of Helicobacter pylori by biochemical and anatomical methods is obligate. Among qualitative biochemical CLO-tests the "express-urea" one, produced in the Rostov dealer Scientific Production Enterprise "Source System", was used. This method differs from other tests by the following properties: the urea activity determination result is evaluated in 5-7 minutes after gastrobiopates being placed into the test solution; after the evaluation of Helicobacter pylori contamination of the gastroduodenal mucous the biopsy samples placing into other solutions for the following anatomic study is possible.

The obtained findings on every patient (136 persons) having been treated according to the above-mentioned scheme have let us prognosticate that only 14% of them will need surgical service in the future. All the patients were put into dispensary observation list, got antiulcer prophylactic treatment and examination (endoscopy, pH-metria, the VNS and gastric motor activity) regularly. Remote results from 4 to 11 years testified that only 6 persons from this group were subject to surgical service.

Comparing the hemorrhage complicated gastroduodenal zone peptic ulcer disease patients' examination and treatment results on a traditional scheme (170 persons) with the results of treatment of 163 patients examined and treated on our scheme, we have come to the conclusion that due to the examination and treatment of patients on our scheme we managed to decrease the number of surgeries by 52,2%

and the lethality – by 21,4%. Thereat we think that the surgeries executed without strict indications and stomach functions features regard can lead to the development of a great number of pathological states demanding persistent conservative therapy or reoperations.

Thus, the hemorrhage complicated gastroduodenal zone acute peptic ulcer disease patients' treatment results allow coming to the conclusion that to determine the treatment policy of such patients the application of these examination methods are obligate.

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RESEARCHING OF NERVOUS VESSEL'S SKIN REACTIONS IN YOUNG TRACK AND FIELD ATHLETES

Chernyakin D.V., Aleksanyants G.D.

Kuban State University of Physical Culture, Sports and Tourism, Krasnodar, Russia

The process of training and competitive activities while practicing track-and-field athletics in young sportsmen is always connected with intensive muscle loadings, strenuous exercise, that cannot help reflecting on the functional status of the vegetative nervous system (VNS) as it takes part in the adaptive mechanisms of physiologic processes regulation. One of the important factors reflecting the VNS work level is the skin neurovascular apparatus state. For the estimation of the skin neurovascular apparatus the reactions emerging in response to a mechanical irritation and characterized by the appearance of differently colored lines, i.e. dermographism, are used.

The purpose of the research was to study the skin neurovascular apparatus physiological maker in young athletes during the pre-season of the yearly training program.

When investigating local dermographism (the pencil for dermatographs of V.A. Madorsky) the time of its emerging (the dermographism latent period), and also the duration and color were taken into account. The force of pressure of the dermograph on skin made 200 and 500 grams. The skin response reaction on the pressure of 200 grams was considered. The rest observations were used only for defining the adequacy of the skin reaction to the irritant force.

31 young track-and-field athletes aged from 12 to 16 (the second junior – the first senior degree) took part in the examination. Different factors of the latent period norm and dermographism duration, according to different authors' findings (V.A. Grebennikov, V.D. Vetchinkin, 1985; P.Ya. Yakobson, 1994), de-

pending, as it seems, on the difference between the research methods of this factor, served the basis for the local vascular reactions investigation in 30 apparently healthy coevals of the control group.

As the result of the carried out control studies and statistical treatment of the findings the dermographism latent period duration norm, made $5,1 \pm 0,9$ sec, and the duration of its existence from 4,5 min to 8 min have been determined. Considering the fact that it is inappropriate in practice to determine the duration of the dermographism latent period in fractions of a second we think it is possible later on in our further work to take the latent period of 4-6 sec for the norm. The dermographism latent period duration characterizes the skin neurovascular apparatus affectability. The analysis of the findings testified that in 17 (54, 8%) examined athletes a normal affectability of the skin vasomotor system was observed, in 12 (38, 9%) examined sportsmen – the skin vasomotor system affectability was lowered, and in 2 (6, 3%) – it was increased. Summing up, it is necessary to note that the lowered affectability of the skin vasomotor system in young athletes is registered considerably more often compared to the increased one. In accord with the dermographism duration the following results were obtained: in 20 (64, 5%) examined persons a normal in time dermographism (the dermographism duration of 4 min 30 sec – 8 min); in 9 (29, 1%) – an inert in time dermographism (the dermographism duration of not more than 8 min); in 2 (6, 4%) examined persons – a quickly disappearing dermographism (the dermographism duration of 1-4 min 29 sec).

Thus, when investigating the latent period and the duration of dermographism in young athletes, in more than a third of them the skin neurovascular apparatus functional status disturbance has been established.

The study of dermographic lines' coloration in young athletes and persons of the control group didn't make it possible to register a substantial difference. Practically in all the examined the lines colored from pink to red emerged at the dermograph pressure of 200 and 500 grams. That is, the color study in young track-and-field athletes hasn't given fresh information for the judgement about the skin vasomotor system functional status.

The changes on the part of the skin neurovascular apparatus in young track-and-field athletes detected by us testify to some extent to the adaptation mechanisms of physiological processes regulation, the vegetative nervous system in young sportsmen in particular.

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*Shot report***MORPHOLOGICAL CHANGES OF GUINEA PIGS' SKIN EXPOSED TO X-RAYS**

Melchikov A.S.

Siberian State Medical University, Tomsk, Russia

The analysis of experimental animals' (guinea pigs) different focalization skin derma structures' morphological changes on 1- 60 days after X-rays exposure finish was carried out.

In the comprehensible literature the available data about skin derma changes at the X-ray radiation action are extremely few and contradictory, due to what it becomes interesting to carry out an investigation dedicated to the cells' factors changes study at their being exposed to X-ray radiation.

The investigation was carried out on 81 mature male guinea-pigs weighing 400-450 g, 51 of which were used in the experiment and 30 – served as the control. Maintenance and work with the experimental animals were carried out in accordance with the rules accepted by the European Convention about the defense of vertebrate animals used for experimental and other scientific purposes (Strassburg, 1986). Before the experiment the guinea-pigs 3-5 times were subject to a "false" effect with the apparatus on, but the irradiation off, to exclude the stress factor. The experimental guinea-pigs were exposed to single general irradiation (dosage – 5 Gy, 0,64 Gy/min, filter – 0,5 mm SI, voltage – 180 kV, amperage – 10 mA, focal distance – 40 cm). The radiological apparatus "RUM-17" was used as a radiation source. The irradiation took place at one and the same time of the day – from 10 to 11 o'clock in autumn-winter period. Excluding the animals from the experiment and sampling the materials were done immediately, in 6 hours, on the 1st, 5th, 10th, 25th and 60th days after finishing the exposure. The flaps of skin were taken from different areas (head (cheek), back, stomach). For the histological examination the material fixed in 12% neutral formaline and then poured into wax, from which 7 mm thick sections were made, which were stained by means of the traditional method – with hematoxylin and eosin according to van Gieson in Weigert modification, - was used. Also a range of histochemical methods was used. For proteins the skin sections were stained with 0,1% water or saturated sulem solutions of bromphenol blue (BPB). Glycosaminoglycans were detected by sections' staining by 1% solution of alcian blue with pH -1,0 and pH -2,5 and the corresponding controls performance and 0,5% solution of toluidine blue for metachromatism detection. For glycoproteins and

neutral mucopolysaccharides the sections were stained by means of carrying out the periodic acid Schiff reaction according to MacManus. The control for glycoproteins and neutral mucopolysaccharides was carried out by the sections' treatment with amylase. For the RNA detection the method of Brache sections' staining was used. A part of the objects for the RNA and DNA detection was stained with the help of chromic aluminous gallocyanine according to Einarson. For submicroscopy the skin flaps were fixed in 2,5% glutaraldehyde in 0,2 M cocadylate buffer (pH-7,2) and post-fixed in 1% solution of osmic acid. All the objects were poured with araldite. Sectioning was carried out on an ultratome LKB-III. Semifine sections were stained with toluidine blue, ultrafine ones - contrasted with uranyl acetate and plumbum citrate, observed and photographed through electronic microscope JEM-100 CX-II (Japan). Hematological control (total count of erythrocytes and leucocytes) was carried out during the experiment.

At the microscopic investigation of the histologic specimen during the first day after finishing the X-ray effect on the part of all focalization regions skin derma cells the decrease, compared to the control, of plasma sensitivity to acid stains is registered. The nuclei of separate cells, including fibroblasts, are rounded off, and in the karyoplasm 1, more rarely 2, hyperchromatic nucleoli become apparent. At submicroscopic investigation from a part of all focalization regions skin derma collagen fibers the osmophilicity degree lowering is registered (fig.1). On the 5th day after the X-ray effect finishing the plasma acid stain intensity of most papillary and reticular dermis cells decreases. A part of the specified cells were expanded, with blurred limits. In the given cells a decrease of the pyroninophilia intensity is observed, that manifests itself as faintly red diffuse coloration, when stained according to Brache. In separate fibroblasts the pyroninophilic substance is detected only near the plasmolemma. Compared to the control, the bromphenol blue water and saturated sulem solutions stain intensity of the most skin derma cells' plasma decreases, that testifies to the decrease of basic and total proteins content in the specified cells. On the 10th day after the X-ray radiation effect finishing at submicroscopy in a range of visual fields changes on the part of collagen fibrils come under notice, which manifest themselves as non-uniform optical density, the fibrils' thinning and their lysis locus (fig.2).

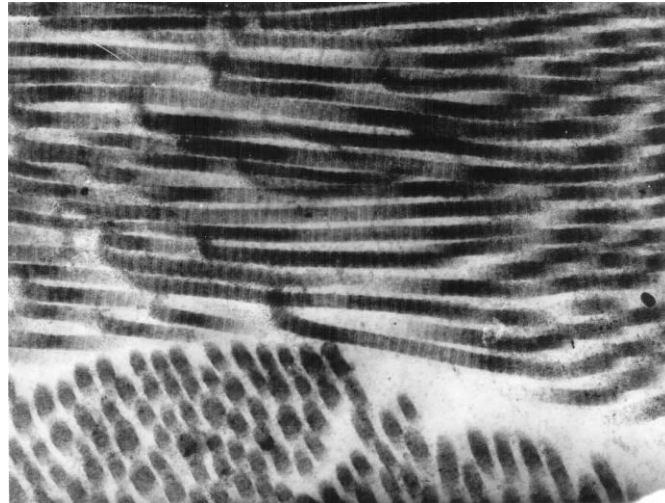


Figure. 1. Fine structure of a guinea-pig's head skin derma collagen fibers. Control. Blown-up 48000 times.

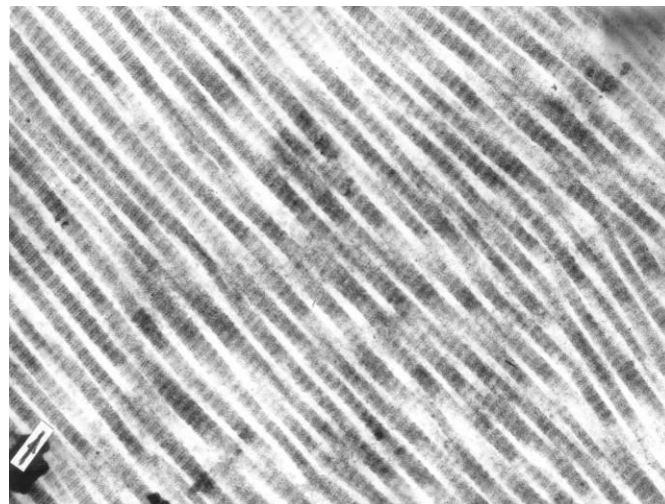


Figure 2. A guinea-pig's head skin derma collagen fibers' osmophilicity degree lowering on the first day after X-ray radiation effect finishing (arrow). Blown-up 48000 times.

In separate fibroblasts located near the specified regions of fibrils intracellularly collagen inspissation forms appear, in particular in the form of globules in the developed cytoplasmic cytoplasmic cavities, which most probably are the cistern of cytoplasmic reticulum (CPR), alongside with this actin-measin cytofilaments are detected. Histochemically the regions of the fibrils' intense synthesis are characterized with fuchsinophilia, while in the collagen fibers disorganization places the pikrynophilia and γ -metachromasia become apparent, which testify to the accumulation of acid glycosaminoglycans (GAG) between the decomposing collagen fibrils. On the 25th day after the X-ray radiation effect finishing in the reticular dermis the increase of acid magenta affinity of a considerable part of collagen fibers is registered, and large, reaching 60-65 μm , fibroblasts are also detected. In the nuclei of the specified fibroblasts chromatin globules are diffused, more often 1-2 nucleoli become apparent, one of which in many cases is dislocated to karyo-

lemma. The plasma of the specified cells is faintly basophilic. In oil glands the plasma of the most cells of cambial layer is faintly stained with eosin, and their nuclei – with hematoxylin. The nuclei of the specified cells are enlarged in size; often have an oval shape, in many cases contain hyperchromatic enlarged in size nucleoli intensively stained with hematoxylin and methyl green, when stained according to Brache. On the skin specimen stained according to van Gieson in separate regions of subcutaneous fat thin collagen fibers are detected. Round single lipocytes macrophage clump is registered. On the 60th day after the X-ray radiation effect finishing a considerable part of collagen fibers is intensively stained with fuchsin. The affinity of nuclei and plasma of the most part of fibroblasts to hematoxylin and eosin and also gallocyanine, when stained according to Einarson, is enhanced, in separate cells expressed so significantly, that it is not possible to detect their detailed structure. In the conjunctive tissue of papillary and reticular dermis, sepa-

rate cells with plasma vacuolization and hyperchromatic nucleoli phenomena are observed.

The findings testify to vivid morphofunctional changes of different localization regions' skin derma

cellular elements observed during the whole observation period (60 days), when exposed to X-ray radiation.

THEORETICAL ASPECT OF PERSONAL READINESS FOR PROFESSIONAL ACTIVITY FROM FUTURE SPECIALIST FORMATION POSITION

Yakovlev B.P., Bogdan I.T.

*Surgut State Pedagogical University
Surgut, Russia*

In conditions of socioeconomic, political and ideological transformations implementation the social significance of their psychological supply grows. A discrete role thereat belongs to the psychological science and practice acquiring in latter days more and more significance in the basic spheres of the society's life activity.

The solution of numerous social-psychological problems is made difficult by the insufficient theoretical and experimental-practical exploration of the questions associated with the psychological readiness ones.

The readiness problem has been in the picture of domestic works devoted to personal self-development problems, the personal potential realization, axiological objectives self-choice, life policies forming-up, in particular (Abulkhanova-Slavskaya K.A., Asmolov A.G., Bozhovich L.I., Dubrovina I.V., Dyachenko M.I., Kandybovich L.A., Zabrodin Yu.M., Zimnyaya I.A., Feldstein D.I., and others).

At the same time an insufficient format of psychological concepts, the corresponding conceptual mechanism and conditions of successful personal readiness formation are observed. It should be noted that there is both a scientific and practical demand for an integrated study of personal different fields' (educational, vocational, sportive) readiness peculiarities in different stages of personhood achievement. A special social meaning is acquired by the revelation of psychopedagogical conditions for the personal readiness formation in the system of education.

The modern objectives of the higher education reforming determine, first of all, the strategy of higher priority attention to the personality of all the subjects of the academic process – both students and teachers. Nowadays the conviction, that the narrow-tactical “dedicated or technological approach” in education should give its place to a wider and

more strategic “learner-centered or humanitarian” one, is being spread more and more.

The learning-educational process of getting higher education in a university is built on the fact that students should be oriented on being taught different subject skills and activities. Many students manifest their passiveness and dissatisfaction with the academic activity, cannot use and develop their motor, cognitive and creative abilities, which their teacher orient them on at classes. The lack of anxiety for active self-development and acquirement of professional knowledge and skills, creative abilities promotion can be associated with the predominance of the technocratic or dedicated training for the present time.

In the dedicated education in the process of academic activity the personal development is hardly taken into account (mainly is declared), the student's anxiety for success, creativity, independence, initiative to solve professional, educational, problem tasks. So, Klarin M.V. gives the following didactic characteristic to the technocratic approach within an education model building (1).

The didactic searching in the tideway of the technocratic approach: proceeds from effective reproductive activity as a self-dependent value; preferentially directed to didactic aims of a low cognitive level; are personally neutral; make an accent on standardized educational procedures and suppose a positive emotional background, but, at the same time, personally neutral character of the student's and the teacher's involving in the

academic process; put the teacher into the position of an operator-teacher (2). The main objective in the dedicated education – is the assimilation of subject-disciplinary knowledge on the teacher's order. In this case, for the pedagogue, the learner (student) is an object for training and up-bringing.

In traditional education the teacher creates means, forms motives, shows aims, organizes conditions; the main trend of this education is the achievement of the required by the programs educational results and total control over the educational content and information obtaining. Such dedicated approach promotes only the development and formation in the learner of "passive-personal readiness"; according to K.D. Ushinsky, they are brought up by creatures "constantly preparing to an activity and remaining dreamers forever...".

At the present time in education the attention is more and more drawn to the didactic technologies in the midway of the learner-centered approach (2).

According to the learner-centered approach, it is important to implement certain psycho-pedagogical conditions in the process of the interaction of the student and the teacher, so that the learner appeared as a full subject of educational-cognitive activity. The main optimal interaction implementation form is the preparation, for the teacher - the professional-psychological preparation, where the prime attention is drawn to the professional development, self-determination; for the learner – the psycho-pedagogical preparation, where the prime attention should be aimed at the personal development. Under the given circumstances an *active personaility readiness* to self-development is formed through the system of "subject-subject relations".

The teaching process organization based on the learner-centered approach means that all the methodical solutions of the teacher, for example, the educational material organization, use of these or those ways and methods, should be refracted through the prism of the learner's personality, his needs,

motives, experience, abilities, activeness, mentality and other individual-psychological peculiarities.

The purpose of our work was the investigation of the student's personality readiness formation peculiarities in self-development and creation of preconditions for professionalism in the context of educational activity.

In the course of an educational process the interests and needs for self-development should be taken into account and the student's personality self-development preconditions should be created. The whole educational process of the academic activity should be aimed at an integral development of a personality, the consideration of its wants and interests in the field of getting higher professional education. The learning-educational process is becoming the process of self-determination in professional-pedagogical culture and education values in the course resting on the learner-centered and activity approaches.

A theoretical study of psychological literature and experimental research testified that the readiness in the conditions of a certain kind of activity – is an extended notion. In accord with the up to date knowledge it can be considered as a many-component and multivariate structure being characterized by certain set of signs for every activity.

The set of readiness signs in a certain kind of activity involves: the ideological, moral, functional, psychological, special (professional) and personal readiness.

The personal readiness is a necessary component for this organic whole, often being decisive for the efficiency and success of an activity. It represents one of peculiar psychic states of an activity subject.

As every other psychic state it is an integral manifestation of a personality, it is always causal, characterized by definite time parameters, has a dynamic (functional) system at its root. It means that, first, all its components are connected between each other; second, its functioning is subjected to the hierarchic principle; third the relations between the components are mobile and each of

them, by virtue of the determining influence of an activity's objective conditions, can be leading.

Joining a large cohort of scientists, specialists working in the field of psychology of personality, it should be emphasized that a successful activity depends not only on their relatively stable qualities, but also on more changeable psychic states. "Every psychic event happens as if against a certain psychic state of a person, which conditions its behavior, and later also its change", S.L. Rubinstein (1954) wrote. Therefore, both at a theoretical, but especially at a practical level the psychological testing of learners should be obligatory analyzed include getting not less than two personality parameters:

- individual-psychological makers of a personality;
- temporary psychic states of a personality, including reactive states.

At the differentiation of individual-psychological makers of a personality or stable qualities of a personality and temporary psychic states expressing them, their dialectic unity should be taken into account for the personality's features can be vividly manifested for a short while in the corresponding psychic states, the personality's stable feature itself appears to be a component of different states, the dominant role being played by it in their structure not necessarily.

Of course, the qualities of a personality have a corresponding effect on the course of psychic states, which, in their turn, influence the formation of personality traits, the professionally important qualities promoting an effective and successful activity among them.

The idea that the qualities of a personality grow from psychic states and the developed trait becomes the condition for new states formation was offered by N.D. Levitov (1971) already.

Thus, a leading specific activity results, on the one hand, in the formation of specific personality traits, and on the other hand, - in working-out of temporary subjective states, which not only promote the efficiency of an

activity, but determine the behavior of the activity subject as a whole.

One of important aspects while analyzing the inner conditions of an activity is an organic alliance of the substantial (qualitative) and energetical (quantitative) analyses of the personality structure as a whole, its separate components and their psychological manifestations. To provide such integrity in the personality activity source – the activity motivation, understanding is of prime importance. The simultaneous sighting of the substantial and energetical activity aspects, and the personality structure accordingly, is specific for their psychological study (Aseyev V.G., 1976).

For every kind of activity there is a certain set of substantial components (signs) – i.e. a specific syndrome including the majority or minority of personality characteristics.

The theoretical or experimental studies on psychology of personality served the conventional basis for the establishment of structural components of the personality readiness state syndrome for practical professionals-psychologists. The components are:

- well-developed intuition;
- self-consciousness;
- high level of abstract-logical and social mentality;
- positive moral qualities;
- facilitiveness;
- high level of empathy;
- role behavior wide range formation.

Such a personality readiness cannot be developed at a large scale, however, proceeding from the premise that the profession of a practical psychologist has actually become a very popular one, it is necessary, as scientists consider, to acknowledge that many specialists do not originally possess those necessary individual qualities, which further on allow making their work effective and professionally literate.

An essential practical importance of the personality readiness state in activity is in the fact that it represents a background, which, on the one hand, psychical processes aimed at the orientation of a subject in situations

and conditions of the activity, adequate to these conditions self-regulation of actions, thoughts, feelings, behavior as a whole, solution of specific problems leading to the objective achievement, take course against. On the other hand, it is well known in psychology that stable personality traits grow from psychic states, and the developed traits become the condition for the formation of new the states providing the efficiency and success of the activity.

Thus, a certain activity (professional, educational, sportive) lead, first, to the formation of specific personality characteristics; second, to working-out of the readiness type personality states, which not only promote the efficiency of the activity performance, but also determine the behavior of a person as a whole.

It is readiness that, according to N.S. Pryazhnikov, should become the main objective of professional and personality self-determination (the synonyms of which are self-actualization, self-realization, self-fulfilment, self-transcendence). N.S. Pryazhnikov (2001) writes: "The main (ideal) objective of professional self-determination is gradually to form in the client the inner readiness to plan, correct and realize the perspectives of his development (professional, life and personality one) independently and consciously" (3).

The relevance of the topic is determined by the process of study and formation of conditions promoting the personality and professional growth.

Under the personality readiness we understand an individual-psychological directivity, tuning to voluntary activity, mobilization of abilities to active and rational skills, actions. The efficiency of personality readiness formation methods and means will depend on the degree of theoretical statements working-out by our laboratory and the system of estimation and criteria and regulation of psychic states and personality traits.

The personality readiness psychological theory must be founded on methodological statements of the determinism principle

and learner-centered and activity approaches. The working-out of scientific humanistic paradigm about the place of personality readiness in the academic process and professional activity will be of an essential value.

That is why the scientific interest will be focused on the investigation of various kinds of readiness, its structure, component representation and mechanisms of transition, transformation of psychic states into stable personality qualities in conditions of academic and professional activity.

The analysis of theoretical and methodical literature allowed us to detach the components of students' personality readiness formation and to define the psychological-pedagogical conditions for the formation of these components. Their close relevance and supplementation with each other will promote the effective self-realization of professional actions and personality manifestations of students at sessions on the selected speciality. It will be manifested in the fact that the pedagogical skills' separate component formation realization occurs only with the organization of all the complex of conditions. Psycho-pedagogic conditions play a key role in the formation and development of the marked by us components.

The most important psycho-pedagogic conditions for the student's personality readiness are:

1. *The transfer of the student from the position of an education and upbringing object into a self-development subject.*

This condition will be implemented if:

- a subject-subject interaction of all the participants of the educational process has been guaranteed;

- the situation of success in the academic activity has been created, that conditions the provision of positive growth experience for a student in the group's and teacher's presence, that stimulates a further work of the personality over himself and is the source of self-development and self-bringing-up;

- the interpersonal relations, which suppose the creation of mutual understand-

ing, kindness and openness at classes, have been formed. A teacher should become a true tutor having interest and respect with students.

2. The personality readiness specific components representation.

The personality readiness represents a form of superstructure, a system reaction on the corresponding real or predicted situation, the information content of which is integrated into a mental model providing such a reaction. The quality of the state is determined by the degree of its adequacy to the activity implementation content and objective conditions. The personality readiness involves the following components:

- motivational – the interest, aspiration to achieve success, need to achieve the aim;
- cognitive – the understanding of problems, duties, knowing means towards the end, skills to forecast own activity;
- emotional – the confidence in success, inspiration, feeling of responsibility;
- conative – the sense of purpose, i.e. subjection to a purpose, mobilization of forces, concentration on the problem, abstraction from troubles, overcoming doubts;
- communicative – the constructiveness and effectiveness of contact interaction with people and environment, ability to gain, support and develop business and personal contacts.

Ultimately, the state of personality readiness is formed by means of many specific components – the phenomena, every one of which can be dominant, and then the given component will have an effect on quality features of the state derivative from the interaction of internal and external conditions of life.

The carrying out of students' personality readiness main components diagnostics supposes that at the educational process organization the individual development features of students should be taken into consideration to the maximum. This is the motivation-conative relation to the academic activity; the success achievement and trouble avoidance motivation; the cognitive need and

creative activity presence in getting knowledge and academic training level in the field of psychology; the ability to self-education, self-development, self-bringing-up processes on the basis of reflexive thinking, consciousness, understanding, rethinking of the process and results of own activity; the level of methodological and practical knowledge and skills, etc.

3. The creation of personal development situations at learning sessions immediately.
The given condition supposes:

- a contact between the teacher and student through a dialog, which supposes the equality of psychological positions of the two interacting sides. The situation of double-sided interactions means an active role of all the sides involved into the communication. The dialogical interaction supposes:
 - the education space retargeting to the personality sphere of students;
 - a "game" form for creation of personality development situations with active use of interactive learning and control methods, change of role positions;
 - the application of means and methods for learning motivation formation. The educational process is aimed at the formation of positive motivation in its reinforcement by means of activeness of the person itself;
 - the application of problem educational methods in adoption of scientific knowledge system and results, the process of getting results, formation of cognitive independence and development of creativity of the student.

4. The education and culture of axiological potential development through one's own activity. An individual develops in the process of its own activity. In the basis of the activity approach in education the personal inclusion of every student into the process lies, when the activity components are aimed and controlled by it.

The personality approach – is the inclusion of students into the educational process organization. The problem setting at a session, planning its solutions, further realization and evaluation of the implemented ac-

tions are fulfilled together with the teacher; the creation of conditions for the choice of session conduction forms.

5. *The students' reflexive skills development updating.* The educational process efficiency depends to a large extent on how actual the students' reflexive skills become (depth, latitude, complexity, verity). At pedagogical skills realization the reflexive actions of students become an integral component at every stage of their activity organization, that promotes the personality development and self-cognition process activation.

6. *The readiness of the teacher to the learner-centered approach realization.* The teacher's personality readiness requires his psychological skills (communicative, organizational, gnostical, constructive) development realization:

- to draw attention to the activity subject or relations during the communication with educatees;

- to instrument the recognition of both the educatee and educator to differences in opinions, judgements, tastes, abilities – then the communication with children becomes interesting and spiritually rich;

- not to resort to direct and open appraisal of the educatee, to use the method “I – information” when evaluating him, then the learner's self-confidence consolidates and his activity and self-evaluation grow;

- to manifest the empathic understanding of the student, respect and kindness, to express sympathy to his life, feel with his success and misfortunes;

- to underline the unique character and soleness of his personal “I” – then the status and self-control of this educatee in the group grow.

7. *The ratio of personality and situational factors in behaviour determination.* The classical research of Hartshorn and May (1928) testified that human behaviour depends not only on stable personality traits, but also on situational conditions. However, can external conditions, besides internal ones, influence the behaviour, if one bears in mind the following important position of S.L.

Rubinstein: external conditions act through internal ones (4)? How after all one can combine the oneness of personality traits and “external situations” in the personality theory (for example, in personality integration itself) still remains out of view of investigators. The uncertainty of this most important problem has found out both “personality traits” theory and situational personality theory to be invalid with all acuteness. Having arisen in psychology and not been solved yet, the dispute over the comparative role of different behaviour factors (and life as a whole) can be solved dialectically on the basis of a certain new personality theory considering the differentiating of situations in the process of individual personality structure development. Such a theory should be built at a higher consistency level and include into the personality integration not only personality traits, but also the variables of situations in their relation with these traits.

The comparison and a more detailed further analysis of the given signs allow drawing a certain way of the personality theory and the corresponding psychognostic supply perspective development.

8. One of the realization conditions of the learner-centered education in a higher institution can be *the organization of psychological preparation of students and teachers.*

As the principle directions of the preparation to the activity of teachers and students in a higher establishment the methods of psychoprophylaxis, psychognosis, psychocorrection, psychological consultation, psychological enlightenment and other methods should be considered and realized. The generalization of psychological and professional counseling experience through a dialog, for example; holding of objective-reflexive trainings and interdepartment scientific-methods seminars; rendering individual counseling assistance to the student are of positive value. The fact is that the prevailing at a higher establishment group session forms including group games and trainings, etc. are more applicable for brainwork training and not for intimate personality sides' development. That

is why the student's personal contact with a qualified specialist psychologist-pedagogue can be an indispensable means of the student's individual support, if he himself is in want of such a support and has realized that.

9. An important condition for the personality self-development is *control and self-control*, which represents the feedback in the personality development. The effective personality diagnostics should rest on the information about the personality manifestations not in a certain, comparatively narrow, kind of activity, but in life as a whole, i.e. bear a system-style character (see above about the corresponding principle).

A creative interest to the teacher's professional activity personality readiness investigation testifies to the given problem topicality. Together with that the certain professional activities personality readiness components, inclusive of the concurrent activity of subject-psychologist, remain insufficiently studied. The method of the selective formation of the future subject-teachers' psychological readiness for their practical activity as

early as in conditions of higher establishment training requires renovation.

Currently, the diagnostics problem, the development of the personal readiness state criteria, means and methods, that is necessary both for the creation of a theory and practical purposes – the control and readiness control, the forecasting, projecting of valuation in problem solving, the professional selection, special psychological training, the activity efficiency and success and psychic health provision, still remain not less important.

All this set of problems needs further efforts for their settlement.

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*Materials of conference***PLACE AND ROLE OF HIGHER SCHOOL SCIENCE IN FORMATION OF REGIONAL INNOVATION POTENTIAL**

Belokrylova O.S., Berezhnoy I.V.

Southern Federal University, Rostov-on-Don, Russia

The innovation potential of a region involves a formed system of the judicial and business stimulation of the innovation activity and immediately the potential of innovation developments of Higher School, enterprises of small and medium business on regional business life branches' modernization. As in other spheres the innovation potential development can be carried out by two probable scenarios – pessimistic (inertial) and optimistic (active) ones. The realization of the last, allowing accelerating the processes of the regional innovation business life development considerably, is the most advantageous. In connection with this the development and realization of regional enterprises' and organizations' innovation potential extended reproduction governmental stimulation measures and also the concentration of financial resources of the regional budget on the support of priority projects making a synergistic effect for the whole regional business life (power engineering and saving, communications, nanotechnologies, human resources development, etc.) are required. As the maximal sustainable growth rate can be achieved only when introducing innovations, it sets the problem of the passage from the simulation investment growth to the innovation one, of the "innovative quality" infusion to the business life of the region.

The Rostov Region – the main scientific and industrial area with the highest concentration of Higher School and sectoral research in the South of Russia – desperately needs the integrated into the national one regional innovation system formation process finalization.

Due to the spontaneous (self-development of scientific and industrial institutions and small enterpot) and organized (implementation of regional and federal purpose-oriented programs, creation of legal environment and elements of innovation infrastructure, etc.) formation of the innovation potential a favourable situation for the innovation sector share increase in the economy of the Rostov Region emerged; the base of the sector being made up of scientific educational institutions (universities, research institutes, design centers), industrial institutions, small innovation enterpot. An important factor characterizing the innovation activity is the positive dynamics of the investment appeal rating innovation component. Thus, in 2005, according to the "Expert RA" rating agency's estimates the Rostov Region gained the 11th place among 89 subjects of the Russian Federation on the innovation potential.

The Rostov Region has got a well-developed scientific and technological component of the innovation potential:

- 95 organizations carrying out research and development works (54 scientific and 15 engineering organizations, 14 higher education institutions, 12 technological subdivisions in industrial institutions);

- 87 state and non-state higher and secondary professional establishments, 350 educational institutions of staff training and retraining;

- 3 industrial estates, RAS research center, a range of department and intersectoral information centers, consulting firms, etc.

- the SFU technology transfer center.

The higher school innovation potential is characterized by a high activity. Thus, the Southern Corporate University (SCU), having combined the RSU, TRSTU, SRSTU (SPI), executed research and development works to the amount of 500 million rubles in 2005, the Multi-Access Center of the SCU on nanotechnologies (80 million rubles) was created. In 2006 the TRSTU received 324 million rubles for the innovative education development, and the Southern Federal University creation within the framework of the RF National Education Program guarantees the attraction of additional financing in the amount of 3 billion rubles in 2007 and 2 billion rubles every year in the following two ones. The Rostov Technology Transfer Center (RTTC) combining the potential of the SFU, SRSTU (SPI), DSTU, providing the innovation commercialization through transferring to industrial institutions. However, the innovation breakthrough provision requires the development and implementation of the region's innovation potential extended reproduction mechanisms. The current situation is characterized by an independent development of the applied science and production and caused by the lack in the Rostov Region of the innovation conducting network as a necessary infrastructural component of the extended reproduction of the region's innovation potential providing the market high technology production demand satisfaction by joint efforts of research, commissioning organizations and industrial institutions. The main structural elements of the innovation potential extended reproduction system are:

- the knowledge production subsystem – higher school science, first of all;

- the professional training and educational sphere providing the human potential formation;

- the innovation production and service subsystem;

- the innovation infrastructure including the channels of innovation potential reproduction financial provision.

As an innovation infrastructure system forming part organizationally providing regional innovation potential extended reproduction we offer the creation

of the Regional Innovation Center (RIC) of the Rostov Region – an organization, with which the Rostov Region Authority, on a competitive basis, will make a government contract and which will be committed to work on the innovation process organization in the region. The RIC activity is aimed at the regional innovation processes' activating and overcoming the effects of the preserved trend of the system investment-innovation crisis. The RIC renders expert, information-marketing, analytical and other services. The RIC is called to coordinate the activity of technology transfer centers (TTC), engineering and patent centers (EPC), innovation-technology centers (ITC), industrial parks and other innovation activity subjects financed at the expense of the regional budget.

The holding block groups of the regional innovation infrastructure are the existing and actively developing on the higher school basis academic scientific-innovation complexes, in which the environment for commercial development of innovations in scientific and technological and educational spheres. At the infant stage an important mechanism of the venture capital procurement into the regional innovation system is the creation of the Innovation Fund in the partnership with the Rostov Region Authority.

At the present time the institutional-legal framework of the innovation potential extended reproduction and its use to a large extent consists of general enunciations not letting develop initiative in the priority activities on this basis. For the purpose of legislation concreteness promotion in the innovation sphere it is advisable to fix the priority of getting a state support by the innovation-active enterprises and organizations. For example, even the increased by the RF CB amount of budgetary resources used not in a competitive basis doesn't allow the SFU scientists to get more than 100 000 rubles per quarter on the won intra-university grants.

It goes without saying that it is necessary to adopt a legislative act on innovation activity. Thereupon it is offered:

- to limit the public sector of science with the institutes carrying out the research of the world's level or servicing the public administration and state-financed organizations – healthcare, education, ecology, defence and safety, etc.;
- to give the research institutes retained their scientific potential to higher school for the purpose of research universities formation;
- to create advanced research centers on a competitive basis;
- to pass from subsidization to crediting with the innovation promotion;
- to create technology transfer centers in research institutes and universities;
- for the innovation activity stimulation:
 - a) to release the profit aimed at the new technologies' implementation and research and develop-

ments' financing from taxation within the regional wage limits;

b) to support the creation of small science-intensive firms with concessional taxation within the regional wage limits;

c) to apply accelerated amortization of tangible and intangible assets;

d) to provide public and private insurance of investments into innovation activity;

e) to assist mass creation of small starting firms by the seed capital assignment (by the experience of the SBIR American program), tax concession, rendering judicial and information support;

- to make provisions in the regional budget estimates for science and innovation managers' training regional program implementation or to specialize the managers' training in the SFU and RSEU in this sphere on the Federal program.

Within the active innovation development scenario's framework the priority development of "knowledge production" environment, the research sector competitiveness and priority area developments provision, the creation of effective innovation infrastructure and stimulation of large-scale engineering modernization of economy branches are needed. For the active scenario realization it is required:

- the concentration of budgetary and extra-budgetary resources meant for research and development works' and science-intensive projects' financing in priority area;

- the provision of new high technologies and their demand information dissemination to enterprises and organizations of non-financial sector of economy.

Taking into account the being formed development trends there is a probability for the Rostov Region to raise its role as a knowledge (not technologies) provider. In this case the positive effects from the produced knowledge will mainly fall at foreign economies or other subjects of the RF. The entrepreneurial sector demand promotion for innovations will be generally manifested by the expansion of foreign and other-regional technologies' imports by local companies, that will elevate the "impoverish" risk development. In this case the innovation sector development capitalization will take place mainly out of the region (in Moscow, St.-Petersburg, abroad).

The shortage of qualified managers, patent specialists and lawyers for the realization of intellectual activity objects (IAO) use effective policy in scientific organizations and enterprises restricts the IAO involvement into the economic turnover. The basis for the educational programs implementation should become educational science-based innovation complexes. Together with educational and scientific units the innovation and business structures should be included in the higher school structure. The integration of scientific, educational, innovative and productive activities, natural-scientific and humanitarian training will allow developing and implementing of

the multilevel specialists' training innovation educational programs based on the cross-disciplinary and instrumental technologies of competences formation in the academic process.

The SFU creation on the basis of the RSU, the win of the TRSTU in the national competition of higher professional education innovation programs, etc., testifies to the competitiveness of the Don universities at the national level, and in a range of directions (neurocomputers, bioengineering, and others) – at the international one. In connection with this it is necessary to support the innovation educational products' development and the new technologies' application in the academic and research processes. The development of scientific-academic-production infrastructure (student engineering departments, technoparks, scientific university laboratories, etc.) and educational innovations will provide the passage from the delivery of highly specialized knowledge to cross-disciplinary and complex one, that will result in the retuning of the university environment to the formation of necessary in the innovation economy competences (according to a complex analysis of changing social-economic processes, the skills of organization and running projects, effective search and analysis of different information, practical managerial skills, the ability to research work and practical use of the fundamental and applied research results).

A special attention should be paid to cross-disciplinary directions of specialists' training and retraining for working in the sphere of high technologies. It is important to attract youth to innovation management, to add the disciplines revealing the ways of transformation of the results of investigations into merchandise articles to all education programs of universities. The professional development and training in the sphere of economics and management is carried out at the SFU (faculties of economics, faculty of high technologies, higher business school), SRSTU (NPI), RSEU (RINE) and other universities.

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INTEGRATED INFORMATION SYSTEM OF CONTINUING PROFESSIONAL EDUCATION PROGRAM EXECUTION MONITORING

Berzin A.A., Kurenkov V.V., Pankov V.L.
*Moscow State Institute of Radio Engineering,
Electronics and Automation, Moscow, Russia*

The entry of Russia into Bologna process sets the problem of the continuing professional education work systematization measures carrying out: the continuing professional education (CPE) guidelines regis-

ter creation, the generalization of jurisdictional educational institutions' work results for the purpose of revelation of development trends of the specified activity direction and the process's dynamics correction in accord with the purposes of the realized higher professional education complex development programs.

The results of the work on the integrated monitoring system and information technologies development providing the organization and statistical observation of the Russian higher professional education institutions' faculty's advanced vocational training and realization of continuing professional education programs by them are considered below. The work's actuality is determined by the fact that nowadays the total faculty strength of all higher professional education institutions makes more than 220 thousand people; therefore in the advanced training system about 45000 places are distributed annually, that needs the creation of integrating information record, control and process optimization system. The most important purposeful problem of the specified information system is the computer-assisted creation and support of the integrated informative space in Russia in terms of continuing professional education.

In the system's development phase the analysis, the type definition of relevant information for federal data base forming-up and the unification of information flows structural units were carried out. Nine main statistical reporting forms were developed and the parameters determining the statistical reporting outputs were offered: the organization type, reporting form (advanced training form), fiscal year, variable parameters, etc.

In the next phase the automation processes' software support was developed:

- operational data collection from remote subjects;
- provided information monitoring;
- provision of operational statistical information;
- final reporting forms formation.

The information system bundled software is meant for the information accumulation unification and automation in the sphere of continuing professional education, and also for carrying out the monitoring for the purpose of coordination of extended institutions' and higher education institutions departments', implementing the continuing professional education programs, activities. The created software is designed for the formation of the integrated database on the sponsoring extended education activities institutions' work and the provision of the following functions support:

- information storage in the common distributed database with the information integrity procedures provision;
- accumulation, storage and maintenance of structured information records;

- database updating from work stations concurrently with regard to the data integrity maintenance.

The “client-server” model (Fig. 1), in which the process performed in the client’s part is restricted by representation functions and the applied functions are realized in the software component of the application server, is used at the development. In its turn, the application server is supported by the gateway of exchange with database server, by its information objects. They are stored directly in the database and are

performed on the computer-database server, where also the component functions, which controls the data access, i.e. the DBMS core. The “client-server” model advantage lies in the possibility of centralized, including the server-side remote administration, traffic reduction in the net; possibility of practically unrestricted SHC scaling and application entities absence in the client part, and therefore – no need of client-side renewal distribution.

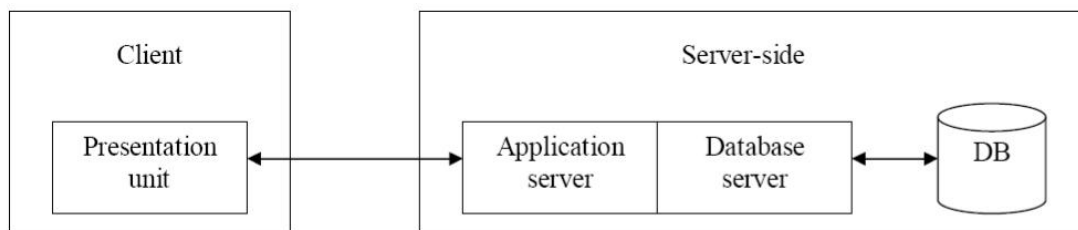


Figure 1. “Client-server” model

The software was created on the basis of the information system maximum work accessibility demands and operator’s position minimum requirements. The operator should possess the user-defined knowledge of work in WWW, the experience of WWW browser use and work with interactive Web-sites. The operator’s work with the program is possible within the framework of any Internet-link.

The possibility of carrying out the advanced training analysis by both higher professional education institutions and those of continuing professional education separately has been realized. The created information system allows analyzing the course of upgrading on different programs and projects, particularly on federal purpose-oriented programs, on the programs of Ministries and Agencies, international programs, etc. Besides, the information system allows analyzing the summarized information on all the programs of qualification upgrading integrally.

An important developed instrument of the monitoring is the operational statistical information enabling to evaluate the process and bring necessary corrections in. With the information system introduction a real opportunity to get and analyze the data from the organizations implementing the advanced training practically in real time will appear; it will be possible to put into effect the very operational control for the upgrading process.

Let us view briefly the variable parameters according to which one can get the statistical information. The following variable parameters types were chosen as the result of the carried out analysis:

- training trends;
- implications for different federal districts;
- listeners’ qualification;
- age categories;
- listeners’ occupational titles.

The information system enables to get the distribution of the listeners having passed the advanced training according to various training trends; federal districts; academic degrees and titles; age categories and official capacities. The created system enables to get and analyze 40 different distributions presented in the form of diagrams which can easily be shown as the corresponding tables. Their analysis allows providing the forecast of the most popular upgrading and the continuing education system development directions. The final data charts also enable to evaluate the efficiency of the professional advancement centers’ work by means of the findings and standards comparison.

In the course of the work execution necessary forms of intermediate and final statistical reporting were determined. The information about the performance of the tasks on the qualification and continuing professional education programs is presented in the form of enlarged direction groups or training specialty charts. At that, there is an opportunity to derive such charts separately for every region, city or the Russian Federation as a whole. All the information can be put in two tables integrating the data according to the specified levels. The data integration level can be given separately on the three levels: city, region and the Russian Federation as a whole. Besides the main output statistical forms the function of representation of complete information about the upgrading results and the extended education program carrying out separately on every institution reporting to the Education Federal Agency about its work in the specified direction was introduced into Federal Database maintenance application program.

The information about the extended education programs execution results is important enough for the analysis of the actual reeducation directions in the society and allows forecasting the most promising ones in the context of further development and main pro-

grams list change. The creation of educational activity monitoring information system in the sphere of the faculty's advanced training enables:

- to form the necessary output statistical reporting including the forecasting of the most popular directions and specializations;
- to create the instruments of professional advancement centers' work performance evaluation.

The solution of the above enumerated problems enabled to develop the innovation model of volume, training directions formation and work organization planning on scientific management and higher professional education institutions' faculties' reeducation and upgrading.

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ADMINISTRATION PROBLEMS WITHIN HIGHER PROFESSIONAL EDUCATION SYSTEM AT INNOVATION ECONOMICS MODEL FORMATION

Butakova M.M., Mamchenko O.P.,
Mishchenko V.V., Sokolova O.N.
Altai State University, Barnaul, Russia

During the latter decades specialists note a considerable rapprochement of developed nations' higher education systems with retaining of the features conditioned by the historical and socio-economic development and demographic situation. The integration of Russia into the world's educational space supposes the national educational system rapprochement with similar systems in other countries with retaining traditions and advantages of Russian Higher School.

Russia actively reforms the Higher Professional Education system, seeks for the most optimal ways, forms and technologies of its development. In December 2005 the "Federal Education Development Purpose-Oriented Program for 2006-2010" was approved by the Russian Federation Government Regulation. The Program provides the Russian educational system competitiveness enhancement relevance; the society development accelerated rate, the political and social choice empowerment; the transfer to the society of knowledge with a considerable expansion of intercultural cooperation. It is underlined in the Program that the native educational system is an important factor of preserving Russia in the row of leading countries of the world and its international image as the country possessing a high culture, science and education level.

The implementation of the denoted in the Program purposes and intents of the RF educational system development requires adequate actions aimed at the activity organization models change and higher educational institutions administration:

- the missions and strategies acceptance and development process initiation;
- the higher education institutions' innovative organization models development and higher institutions' managerial improvement;
- the present-day educational technologies mass introduction into the academic activity;
- the switching to a credit-module organization of higher professional education study programs and building a flexible system of the academic activity control;
- the education quality control implementation and development;
- the financial administration advanced models use;
- the academic activity control information-technology systems introduction;
- the higher institution new personnel management models' development and introduction;
- the educational marketing activity development in higher educational institutions.

The quoted list of innovations can be augmented proceeding from a concrete problem situation and the strategy accepted by the institution.

Serious problems in higher professional education of Russia should be considered as the result of its economic and social development in the context of the world's development. In our opinion, the following problems are referred to the number of such ones:

- the promotion of higher professional education importance in connection with the world's economy globalization and transfer of the leader-countries to the knowledge-based innovation economics;
- the severization of requirements to specialists' training quality within the higher professional education system and the gap elimination between the market demands and higher school graduates training content;
- the severization of requirements to the efficiency of scientific work results use for Russia's share increase in the world's joint intellectual product;
- the creation of innovation activity support mechanisms within the higher professional education system;
- the development of new academic knowledge model based on the applied context of knowledge, transdisciplinarity, education forms' organizational variety and social responsibility for the knowledge produced;
- the formation of a new strategic vision in higher professional educations management.

In conditions of the transfer to a postindustrial civilization, appearing the technology systems combining technological and social innovations into a socio-technical process, the highly qualified specialists' training problems are becoming priority-oriented. A high professional and educational level of specialists – is an important condition for the economy development innovation model formation. Of course, in the

present-day fast-moving world the accumulation of knowledge and its renewal should be performed continuously using different forms of training and retraining, an important place among which is taken by getting higher education. In this connection it is necessary to decide the matter of what ambitions the educational process should face at higher school. Should it be limited with training specialists possessing deep knowledge in prescribed subjects or set the objective of training creative personalities able to solve standard problems? The appearing in the government officials' and economists' training programs of such disciplines as "Innovation Management", "Innovation Business Activity", "Methods of Social and Economic Forecast" – is the result of global changes in the approaches of training specialists, the activity of which will be performed in the period of economy innovation model formation.

The changes in training approaches shouldn't be limited with the composition change of the courses being read. The difficulty is that they involve much more than simple study of new materials and renaming old programs. A full-scale cultural transfer, which in the field of economic and managerial education will mean the research and teaching methods and training technologies change, is required. The existing today education system's orientation to the ready knowledge reproduction by students should be overcome and the conditions for the development of productive thinking guaranteeing the future specialists' readiness for setting and solving complex innovation economy problems should be created. The educational standards require the combination of curricular (class) and extra-curricular (independent) students' work, a significant attention being paid to students' active solitary work preconditions formation. Today it is difficult to hope that a simple teaching load reduction will allow promoting the independent scientific and academic work of students. Under the conditions of insufficient level of higher education institutions' libraries equipment, a relatively poor computer equipment status and the world's information resources access security the education technology change – is an extremely difficult problem. To solve them great financial expenditures and a serious, diligent scientific methodical work on the formation of all students' independent work's elements and components (tests, assignments for submission, cases, practical courses) are required.

Although education is called one of the national priorities, financial problems remain topical. Partially higher institutions try to solve them at the expense of the means got from commercial activity, generally form the paid educational services delivery. Another important source of additional financial resources attraction to higher institutions is grants, borrowed money given on a competitive basis by native and foreign organizations.

The RF Department of Education and Science announced the second round of the competitive selec-

tion of higher professional education establishments introducing innovation educational programs for the purpose of rendering state support for them by means of providing subsidies in the volume from 200 to 1000 million rubles in 2007-2008. The State-run Educational Institution of Higher Professional Education (SEI HPE) "Altai State University", taking part in the competition, considers the development and introduction of its innovation activities on the formation of an integrated scientific-innovation educational park on the basis of the SEI HPE "Altai State University" for the purpose of the continuous multilevel education new models effective realization, the citizens', society's and labour market's demands for quality education satisfaction to be the target of its innovative education program implementation. For the stated objective achievement the following problems' salvation is needed:

- The creation of an integrated scientific-innovation university educational park on the basis of the SEI HPE "Altai State University".

- The provision of an administrative-structural, regulatory, scientific-methodical, financial-economic and material-technical unity of scientific and educational activities on the ground of innovation principles of organization and management.

- The development and introduction of new educational programs on profile directions of training, retraining and qualification upgrading, which correspond to the main ideas of the Bologna and Copenhagen Processes, for the purpose of the Russian professional education competitiveness enhancement in the international market of educational services.

- The cooperation of profile establishments of different level professional education for the implementation of continuous education programs.

- The creation of conditions for the formation of individual trajectory study within the framework of multilevel educational programs.

- Monitoring, forecasting and forming labour markets, educational services and high technologies for the purpose of advanced personnel and scientific-engineering support of progressive advance of Russian economy.

- Carrying out of fundamental and applied research and experimental-designing on the priority orientations of science and education.

- The development of new organizational forms and structures in the field of science, education and innovations.

- The formation of stable relations with specialized industrial and scientific organizations in terms of scientific, educational and innovation activities integration.

- The formation of long term contract relations with strategic partners on the main scientific-educational business lines.

- The international cooperation development in scientific, educational and innovation activities, stu-

dents', aspirants' and young teachers' mobility promotion for the purpose of opportunities extension of their participation in the system of international continuous education and academic initiatives.

- The development of mechanisms of promotion and support of teachers' participation in real scientific investigations and innovative workings.

- The development of modern information technologies in the education and integrated scientific-innovation university park management.

The authors of the article, being the developers of the specified innovative educational program, have offered their variant of innovation changes in a concrete university. In 2007 25-40 higher education establishments of Russia will be able to get the state financial backing, but the indirect effect from carrying out such a competition is manifested for the system of higher professional education in the possibility for every higher institution to find an optimal combination of innovative development forms and methods.

In our opinion, evaluating the higher education development prospects in conditions of innovative economy model formation, the traditions of highly qualified specialists' preparing for practical activity should be retained and the purposeful researchers' training should be developed. The new economics of Russia requires new knowledge and high education level of Russian citizens.

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INDIVIDUAL DEVELOPMENT FEATURES AND LONG TERM ADAPTATION STRATEGY

Vysochin Yu.V., Denisenko Yu.P., Chuyev V.A.
St.-Petersburg State University, St.-Petersburg, Russia
Kama State Institute of Physical Culture,
Naberezhnye Chelny, Russia

At more or less long term exposure of the body to some or other adaptogenic factors different types of long term adaptation or individual development are formed. In the people with the low capacity of inhibitory-relaxation functional system of defence from extreme conditions or factors (IRFSD), irrespective of their age, the adaptation occurs on account of muscle bulk and strength increase against the low muscle relaxation rate, i.e. a hypertrophic type of individual development is formed. At the average IRFSD capacity a transition type, and at the high IRFSD capacity - a relaxation type of individual development are formed. The last type a high relaxation rate and medium factors of muscles' power are indicative of (Vysochin Yu.V., 1983, 1988; Denisenko Yu. P., Vysochin Yu.V., 2004).

At long term adaptation the significant morphofunctional alterations affect not only the neuromuscular, but all the other systems of the body as well. In hypertrophic type people hyperexcitability and low activity of the CNS inhibitory systems are registered, the hyperkinetic (uneconomical) blood circulation type (CT) and extremely disharmonic somatotype prevail. A low economical and operation heart efficiency, a higher energy demands level at rest and testing loads, a higher concentration of energy exchange metabolites, chromaffin and stressor hormones in blood, but a lower noradrenaline and anabolic steroids level at rest and testing loads, low stress- and hypoxia resistance, a lower immunologic resistance, high incidence of disease and traumatism are typical of them.

The relaxation type of development is the best one in every respect. The CNS exciting and inhibitory processes balance, high muscle relaxation rate, excellent motion regulation and coordination, perfect reaction on moving actions, that guarantees the minimization of sport, everyday and street traumatism, are indicative of the relaxation type children. The most economical eukinetic CT prevails in them, a low economical and operation heart efficiency, the minimal energy demands level, a decreased concentration of energy exchange metabolites, chromaffin and stressor hormones in blood, but a higher noradrenaline and anabolic hormones level at rest and testing loads, a high rate of reduction processes and energy resources re-synthesis, excellent physical performance and tolerance are registered. They differ in higher stress- and immunologic resistance; compared to the hypertrophic type children, they suffer from overexertion and diseases 2-3 times as seldom, and, that is of not less importance, have high mental capacity and authentically higher performance in all school subjects.

These conclusions are proved, for example, by our colleague A.Ye. Levenkova's (1998) data about the interconnection of contractile and relaxation characteristics of muscles and central hemodynamics and circulation types factors. The relaxation type young sportsmen (1st group) differ authentically in higher heart functioning and cardiovascular system efficiency as compared to the hypertrophic type sportsmen (2nd group). They also differed essentially in different CT occurrence frequency. In the first group the hypokinetic circulation type occurred considerably more often (59,0% in women; 40,8% in men) and the hyperkinetic one – more seldom (6.8% in women; 14,8% in men); and in the second group, vice versa, the hyperkinetic circulation type was registered more often (42,5% in women; 42,6% in men) and the hypokinetic one – more seldom (17,5% in women; 15,2% in men).

The relaxation type sportsmen, in comparison with the hypertrophic type ones, possess 3-4 times greater longevity, stand exercise and psychological stresses much easier, are subject to overworks of dif-

ferent kind, traumas and diseases 8-10 times more seldom and achieve the highest sport results.

With the skeletal muscles voluntary relaxation rate (VRR) increase and the long term adaptation relaxation type formation the sport traumatism of football players decreases progressively from 100% (at the VRR less than 4,0 1/sec) to 0% (at the VRR more than 9,0 1/sec) and, respectively, their health improves in the same way. Our multiyear research testified that even in football, which is considered to be one of the most traumatic kinds of sport, it is possible almost fully to avoid injuries (excepting those appearing at rough violations of the game's rules by the rival) due to the correct organization of the training process oriented to the CNS nervous processes balance normalization, the muscles VRR increase and the football players' long term adaptation relaxation type formation.

Another experimental verification of these conclusions was obtained at a more profound examination of 197 schoolchildren and their case rate analysis. All the examined schoolchildren composed two groups. The first group consisted of the pupils (132 persons) referring to the first health group and having no cases in the period of the examination. The second group was formed by the pupils (65 persons) belonging to the second and third health groups and having different health deviations (infectious diseases, II-III degree tonsils' hypertrophy, adenoid disease, frequent ARD, ENT organs' and gastrointestinal tract's diseases, allergic diseases, myocardosis, cardiac rhythm and capacity disturbances, etc.).

The comparative analysis of the investigation results showed that healthy pupils (1st group) authentically excelled those of the second group in a range of most important parameters. Nervous processes balance (NPB) of the CNS, VRR of muscles, the capacity of inhibitory-relaxation functional system of defence, the health prediction integral factor and the activity success in hostile environmental conditions. There are no authentic differences detected in the neuromuscular system contractile characteristics.

Thus, it is quite apparently that a low resistance and high incidence of disease in schoolchildren is to a considerable extent determined by the insufficient IRFSD capacity, the CNS inhibitory systems weakness and NPB shift to the dominance of excitation over inhibition and also a low relaxation rate of muscles and the formed, as a result of it, hypertrophic type of individual development, i.e. by the insufficiency of a range of characteristics, which were defined by us as the most important health criteria.

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ABOUT DEVELOPMENT OF MINOR BUSINESS IN THE REPUBLIC OF BASHKORTOSTAN

Kokhanovskaya I.I.
Bashkir State University

Modern social and economical situation in the Bashkortostan Republic calls for a clear-cut specification of priorities, skillful management of resources, concentration of power and credits in most important directions, performance of urgent anticrisis measures.

Bashkortostan state bodies strategic tasks are to realize nowadays industrial, working, natural, scientific and technical reserves fully and effectively, manage structural rebuilt of our economy with an aim to improve its effectiveness, maintain continuous work of the basic state branches industrial, financial, sponsor and technical support of enterprises, producing food and everyday products; to build of people-oriented industry within business activity, support and defense of entrepreneurs; to consolidate financial sphere, credit and monetary circulation; adapt consumer's market; achieve stabilization of reciprocal deliveries, foreign capital, technologies and experience in the dominant economical fields; making foreign economical connections of the republic active. [1, 2]

The dominant directions of Bashkortostan economy development are to raise quality and reduce the price of products made in industrial enterprises; to set new competitive industries, transformation of factories whose products are not sold, fix industrial connections of enterprises, improve ecological situation.

Nowadays there are more than 15.8 thousands of small enterprises in the Bashkortostan Republic[4]. Setting up a great amount of small enterprises would contribute to further development of minor business in the regions of our republic. Foundation and development of small enterprises is the main prerequisite of performing structure rebuilt of the Bashkortostan Republic economy in the modern conditions. Based on development of minor business it can be performed with little financial, sponsor, working and transport outlays at the expense of mass attraction in the industrial circulation local natural and economical resources. Besides new working places will appear to engage population able to work and also opportunities to cover needs for different products [3].

One should solve some key problems for further expansion in the Bashkortostan Republic a small enterprises net and provision of their effective development. One should note that minor business needs permanent state support and first of all lawful confirmation of discount tax obligation and creditation.

For expansion of minor business in Bashkortostan and growth of its effectiveness one needs foundation a state republic body to regulate development of minor business. It can aim at setting up new reconstruction and development of active small enterprises, their financial, credit and informational supply, organ-

ize infrastructure of minor business, giving them state orders.

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**INTERDISCIPLINARY HUMAN ANATOMY
AND HISTOLOGY KNOWLEDGE
INTEGRATION BY MEANS OF MULTIMEDIA
TECHNOLOGIES IN HIGHER EDUCATION
INSTITUTION**

Chrishtop V.V., Ulyanovskaya S.A.
*Ivanovo State Medical Academy, Ivanovo
Northern State Medical University, Arkhangels*

In Russia in medical higher education institutions traditionally anatomy and histology are studied within the framework of different disciplines. It is conditioned by the having formed tradition, methods of the material study and the succession in students' teaching. For the microstructures' development up to the mark another material security, behavior and activity types are required. All this is easier to organize in conditions of the Anatomy and Histology Departments independency.

However, besides a large amount of advantages it forms a range of features in these Departments' activities integration. Their final objective is the formation of an integral idea of human morphology; that is necessary both for other disciplines development and practical physician's work. For example: For an adequate idea of hypothalamo-hypophyseal system work the integration of knowledge about brain pathways and hypothalamus topography, which the student gets at anatomy classes, and knowledge about their cellular composition, which are taught in the course of histology, is necessary; saying nothing of the fact that the data about embryogenesis taught in these courses complement each other, partially duplicating.

In the process of training the integration of fundamental morphological knowledge, in the point of the fact, is carried out in senior courses as far as clinical specialties study. Thus, either in-patient Depart-

ments' teachers or students individually have to be engaged in it. Therefore, for the adaptation of fundamental knowledge to a clinic the Departments issue special teacher editions, introduce courses, conduct lessons in hobby groups. However, these activities do not solve the problem of morphological knowledge integration. For that matter we created a morphological teacher edition “Endocrine system”. In its creation both anatomists and histologists took part. In this textbook the following is according to a single plan: the introduction, macrostructure, topography, blood and nerve supply, minute structure, functions, morphogenesis, a short excursus into clinics; endocrine glands traditionally studied in the courses of Histology, Cytology and Embryology or in the course of Human Anatomy within the framework of “Endocrine system” or organs exercising endocrine function, are considered. Also the textbook is complemented by a glossary of the used there clinical terms.

The textbook is presented in two versions. The first and more complete – the multimedia one - is supplied with original interactive schemes, drawings and microphotographs. This version is executed in the form of web-pages united by hyperlinks. The second – printed – is a more reduced one. It is connected with the fact that not all students can afford having a personal computer at home.

The given textbook when being created was considered by us as an additional one to the main training literature. It can also be used as a reference book for graduates, interns and medical advisers. Now there is a great amount of multimedia aids on human anatomy and histology which elucidate the specified disciplines in the detailed and quality manner. Our textbook together with the available, both printed and multimedia, aids and reference books enables providing interdisciplinary integration of fundamental knowledge about human endocrine system morphology.

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**SOCIAL WORK AS ONE OF HIGHER SCHOOL
SCIENCE UPCOMING TRENDS**

Trapeznikova I.S.
Kemerovo State University, Kemerovo, Russia

Political and social and economical changes taking place in our country, the Russian Federation entry into the world's educational space have set the problem of education concept renewal. The possibilities of Higher Professional Education are being developed, its humanitarian directivity is being enhanced.

Social work is one of new, developing specialties and scientific directions at the same time. The formation of this specialty as higher education one is connected with strengthening of attention to the civil society and constitutional state formation, the exist-

tence of which is not possible without stable social policy.

As the world's experience testifies, in many countries nor programs of social development neither social policy of a state can't do without considering social workers' activity. Specialists in this area are widely used as experts when preparing legislative acts, making decisions by local authorities and social organizations.

Social work as one of higher school trends is necessary to be enhanced; it is also of the current interest to level the eventuating disadvantages (as, for example, needless academicity, lack of practical directivity), pay special attention to training and retraining of social sphere employees, the extraordinary majority of which doesn't have special education nowadays.

It is urgent to expand and perfect the social workers' training program. Besides the subjects of social work proper and also special sections of other disciplines studied by social workers it is required to form the legal, economical and political knowledge base. Particular attention should be paid to the problems of social work management and organization, as an accurately formed social control structure guarantees an adequate social policy of a country.

With the development of social work as a higher school specialty another topical question comes into being – the one of qualification. Nowadays, besides universities as basic educational institutions medical institutes, polytechnic ones, institutes of culture and others are engaged in social workers' training. That is why it is very important to observe unitary standards while teaching specialists of the given profile. The solution of these and other problems will enable to strengthen one of the most promising trends of modern higher school science.

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**FORMATION OF FUTURE PEDAGOGUE'S
DIRECTION IN THINKING IN THE TRAINING
PROCESS AT HIGHER EDUCATIONAL
INSTITUTION**

Shestakova L.G.

*Solikamsk State Pedagogical Institute,
Solikamsk, Russia*

Due to the fact that modern school is aimed at the formation of scientific worldview, direction in thinking, outlook in the learner, it is evident that all the named components and characteristics should be natural for the teacher. Only after that it makes sense to speak about the technological and methodical aspects of the mentioned kind of work. Therefore one of

the problems of a higher educational institution is a purposeful formation in the future specialist of the direction in thinking and ideology adequate to the reality and focused on the perspective, and corresponding peculiarities of his future professional activity.

Nowadays the idea of the world as an integrated organism, all the parts of which affect each other, is more and more widely spread. Nature is meant as an integral living organism, the transformations of which are possible only within certain limits. To learn the today's complex, dissonant, fast-paced world, system-structural, global-evolutionary concepts are needed, among which an important place Synergetics (or the theory of self-organization) takes. Theoretical aspects of Synergetics were developed in the works of H. Haken (German school of laser Physics), I. Prigizhin (Belgian school of dissipative structures), L.I. Mandelstam, S.P. Kurdyumov, G.G. Malinetsky (Russian school of nonlinear dynamics). Synergetics studies complex open unbalanced systems able to self-organization. Such systems can be of different nature, that is why the ideas and principles of Synergetics find application in many spheres of human activity.

From the position of the future professional activity it is necessary to form in the students of a pedagogical educational institution a nonlinear (synergetic) direction in thinking, which we shall understand as the mentality considering the outworld and the human to be complex open dynamic systems oriented on the revelation of universal bonds and relations, functional nature of chaos, instability and chance. Because of the impossibility to settle upon the analysis of the "nonlinear direction in thinking" notion, let us note that it is given on the basis of the works of S.P. Kurdyumov, Ye.N. Knyazeva, L.A. Mikeskina, I.S. Dobronravova, V.M. Darmograi and others.

As the principle characteristics of the nonlinear direction in thinking one can mark the following:

- criticism and abstractiveness in conjunction with the ability to relate the ideal model to the real process;
- logical rigor, conclusiveness and argumentativeness coupled with the readiness to treat a fallback position;
- conation to nature, intentions and phenomena investigation;
- immensity, orientation on the revelation of depth relations and interdependence between the processes and phenomena of different nature;
- manifoldness (an approach to a problem from different sides, the readiness to an objective analysis of an opponent's point of view);
- readiness to actions in the situation of instability, crisis, when it is needed to consider and investigate an apron of probable consequences of the actions, taking into account the degree of their coherence with the inner condition of the system;

- complementarity (the unity of the conscious and preconscious, reasonable and emotional, rational and irrational, intuitional).

Let us consider the possibilities of the content of the State Educational Standards of Higher Pedagogical Education for the formation of the specified characteristics of the direction in thinking in students.

First, the Standard contains the discipline "Concepts of modern natural science", within the framework of which the ideas of synergetics, its matter, principles and concepts can be formed. The content of the given unit in the course "Concepts of modern natural science" can be briefly presented in a cut and adapted for students form as follows.

- Basic notions of Synergetics: order and chaos; reversible and irreversible processes, "time arrow"; chance and uncertainty, fluctuation and bifurcation point, dissipative structure, open unbalanced system; nonlinearity, instability; resonant influence.

- Principles of Synergetics: unpredictability of choice in bifurcation points, its being influenced by not only the present and past, but also the future; the possibility of appearing the order from the chaos; the whole is not equal to the sum of the components, it is a principally new composition; high efficiency of resonant influence; the time irreversibility in bifurcation points, "forgetting" the previous state by the system passed a bifurcation point.

- The possibility of using Synergetics statements for the investigation of various nature systems, its cross-disciplinary and methodological value.

In the process of studying basic concepts and principles of Synergetics it is necessary to form the idea in students that they promote the drawing together of the scientific and humanitarian cultures, have a sizable effect on the scientific worldview formation and outlook ideas of a human being. The person itself acquires a special significance, becomes a real power able to affect the choice of further development trends of the nonsteady world in the light of Synergetics ideas.

Second, a significant positive result can be obtained if in addition to the mentioned content the following two aspects directly oriented on the future professional activity will be considered. the first aspect

lies in the purposeful revelation of the possibilities to apply the ideas of Synergetics in academic fields corresponding to the training profile of the future teacher; for example, the use of ideas and methods of Synergetics in Linguistics, History and Social Sciences, etc. The second aspect – is the revelation of possibilities of a concrete school subject for the formation of a nonlinear direction in thinking characteristics in learners.

Third, a competently organized student's scientific work, which most often is represented by pedagogic and methodological research in a pedagogical higher institution, will have a great effect on the formation of the abovementioned characteristics of the nonlinear direction in thinking. The organization and carrying out a research work (including a student's one) supposes a mastery of a range of skills in planning, realization, analysis and scientific findings admittance. In the most part of students' pedagogical research the student teaching state analysis and use of experimental work elements are assumed. It is this that allows drawing students' attention to the fact that the education represents a complex social organism, which cannot be closed. Nowadays the predominant point of view is the position that the system of education should be flexible, quickly enough adapting to social environment changes. Besides, the learner (who the influence of the educational system is aimed at) is also an open complex system. Therefore the idea of the learner's development, education and upbringing control is persistently sounding in pedagogical theory and practice. The understanding and application of these statements by the student in his research work is one of the necessary conditions of the specified mentality characteristics formation in him.

Reckoning up, let us note that in the submitted article only some possibilities of the nonlinear mentality characteristics formation in a pedagogical higher education institution student have been considered.

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FEATURE OF CRYSTAL FORMATION DURING ELECTROCHEMICAL SYNTHESIS

Vakarin S.V.

Institute of High - Temperature Electrochemistry, Russian Academy of Sciences, Ekaterinburg, Russian Federation

Morphology of the potassium - sodium oxide tungsten bronze single crystals with a tetragonal structure growing during the electrolysis in the melt at 700°C under potentiostatic conditions has been studied. It was supposed that the process of self-organization takes place.

Introduction

In our previous work [1] it was expressed a proposal that the process of self-organization takes place in hexagonal crystals. This conclusion was made on the base of study of the growth rate anisotropy and the morphology of tungsten bronze single crystals during the electrolysis in the melt. The mechanism of such self-organization exists to be the selection of single parts of crystal according to their electrical conductivity.

It is the interest in detailed study of crystal growth of another structure which will allow us to make a general conclusion in respect with the possibility of self-organization of tungsten bronzes in growth process.

Experimental procedure

The bronze was obtained by electrolysis of the 0.325 K_2WO_4 - 0.325 Na_2WO_4 - 0.35 WO_3 melt. According to our studies this bronze is isostructured to tetragonal bronze K_xWO_3 .

During the electrolysis the temperature of 700°C was kept. The wires (a copper and platinum) were used as a cathode. They were previously vacuum sealed by melting into refractory glass and then the ends of the electrodes obtained were polished until all the scratches were disappeared. A tungsten wire covered with bronze layer of the same composition as electrodepositing one on cathode was used as an anode and as a reference electrode.

The structure of bronzes and crystal faces were determined by using the "DRON-3" model diffractometer. Sometimes optical researches were used for faces definition.

The morphology of faces was investigated with the "Camebax" installation.

In the experiments of bronze single crystal growth a two - pulse method was used. At first a pulse of a constant magnitude (140mV) and duration (1 s) was applied to the cell. At those pulse parameters a bronze single crystal was nucleated on the cathode. Then the second overpotential pulse was applied which supported the crystal growth. The second pulse magnitude was varied in the course of the experiments from 0 to 110 mV with a step of 5-10 mV.

Results and discussion

Fig.1 shows the scheme of crystal habitus changes in the overpotential range from 30 to 90 mV. The detail description of crystal refaceting was made in our work [2]. In this work some peculiarities of crystal growth of K-Na oxide tungsten bronzes with a tetragonal structure were studied. In particular, the decreasing of the crystal growth rate in the $\langle 001 \rangle$ direction during increasing of the overpotential from 40 to 50 mV was found. It was established that these effects are connected with refaceting of the crystal apexes.

Simultaneously with determination of crystal faces its morphology was investigated with the purpose to find out of their growth mechanism. $\{051\}$ faces have a rough surface that promotes fast growth, but $\{001\}$ face, which appears after overgrowing of $\{051\}$ faces, is smooth. The growth of such face goes by the layer mechanism. It remains smooth up to 45 mV then the forms in a kind of "snails" appear on it. Further increasing of potential up to 50 mV results to the growth of these forms. Simultaneously with occurrence

of "snails" the faces $\{031\}$ appear. During increasing of overpotential the share of these faces is increased, but they always remain porous. According to our investigation only faces $\{031\}$ and $\{110\}$ exist in the monocrystal in the overpotential interval 50 - 90 mV. It should be noted that irrespective of

overpotential the faces $\{110\}$ have an identical morphology. On photos we see the growth layers extending in $\langle 001 \rangle$ direction. Overpotential rise up to 90 mV results to overgrowing of $\{110\}$ faces and transformation into bipyramid.

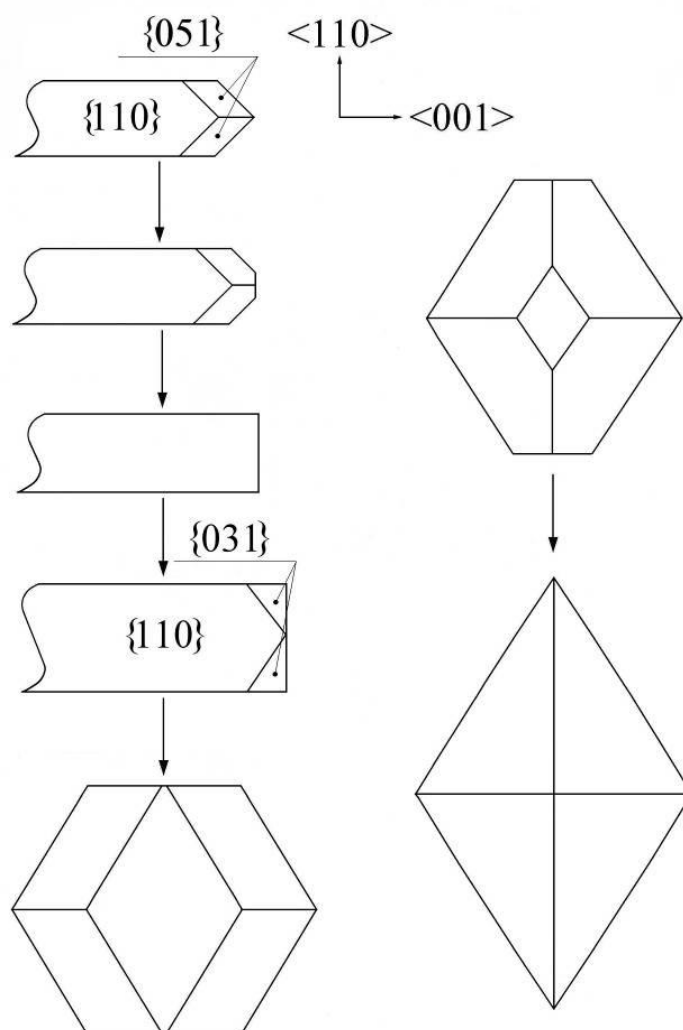


Figure 1. Scheme of crystal habitus changes in the overpotential range from 30 to 90 mV.

Experiments show that bipyramid is steady in a comparatively narrow overpotential interval 90 - 110 mV. It was found that the overpotential rise above 110 mV results in the loss of stability of the plane growth front of the $\{031\}$ faces. The formation of many ledges on these faces occurs (Fig. 2), then during the growth process the ledges

transform to tetragonal needles elongated in the $\langle 001 \rangle$ direction. Their side faces are the $\{110\}$ planes and the upper base is the $\{001\}$ plane. These needles have no azimuth disorientation and due to it they intergrow to form a regular crystal (Fig. 3). Upper base $\{001\}$ of this crystal becomes comparatively smooth (Fig. 4).

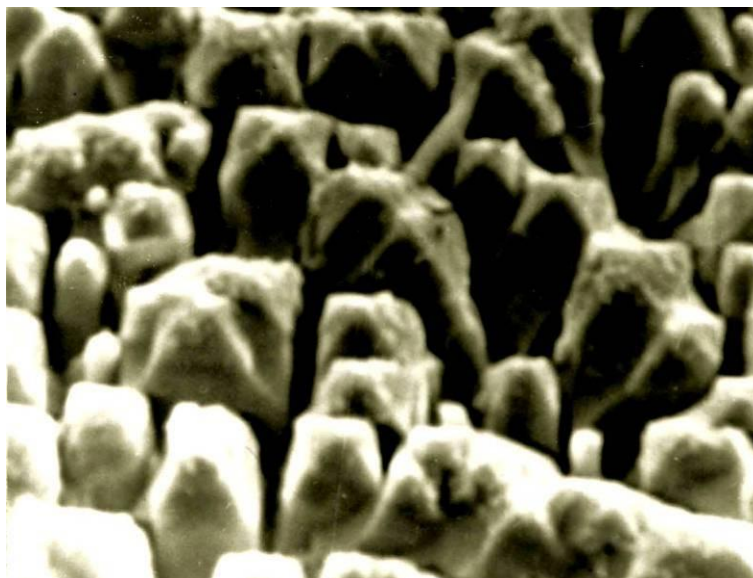
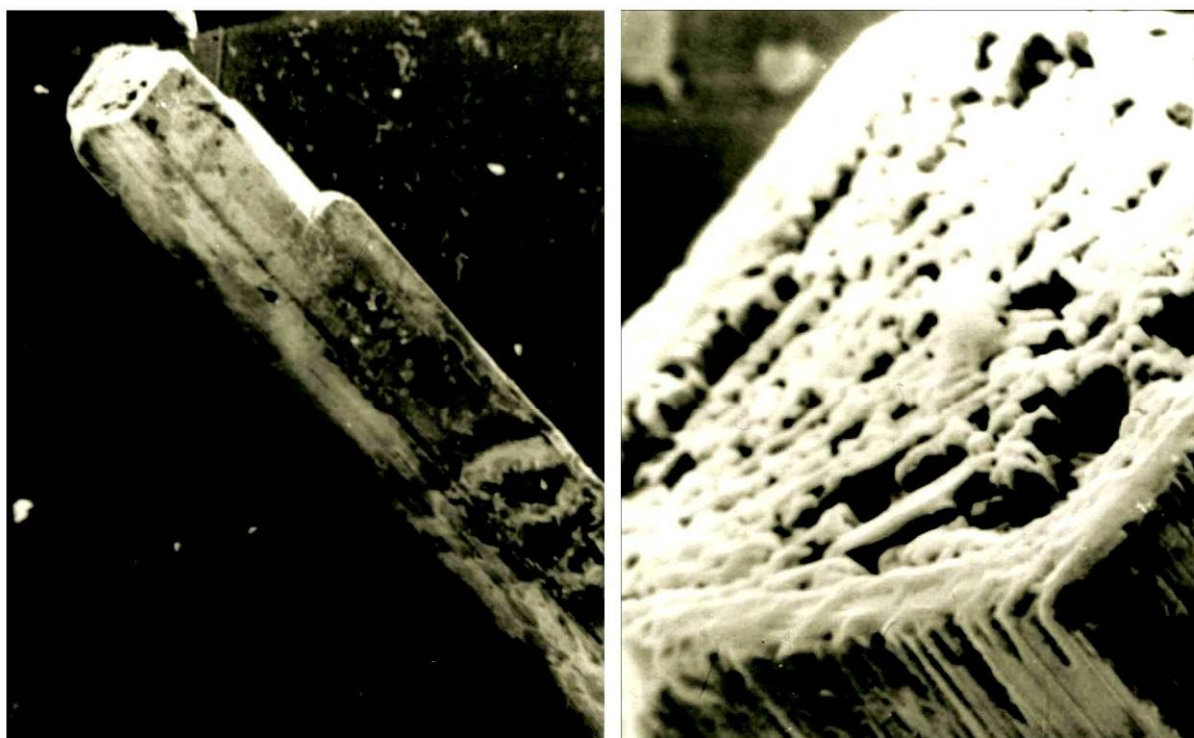


Figure 2. Morphology of the bipyramid $\{031\}$ face at the moment of the loss of stability in the plane growth front (x4000).



a

б

Figure 3. Regular crystal obtained from the bipyramid at 110 mV (a - x100, b- x800)



Figure 4. Morphology of the prism $\{001\}$ face formed by intergrowth of separate needles (x6000).

Conclusion

In the present work the morphology of monocrystals of oxide tungsten bronzes with tetragonal structure growing by electrolysis of molten salts has been studied. It was established, that morphology of crystals depends on overvoltage.

The process of formation of many needles on the crystal surface is similar to the process in hexagonal crystals. Moreover all

of this appears only at definite overpotential values and so we can conclude that the process of self-organization takes place in tetragonal crystals too.

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DYNAMIC INDEXES OF DOUBLE-WAY FEED MACHINE AT DIFFERENT FREQUENCY SUPPLY

Aristov A.V.

Tomsk Polytechnic University

The features of a double-way feed machine performance in the operation of periodic reverse at different frequency supply are considered. A comparative valuation of the system's transient indexes and an electric machine parameters and the load for asynchronous and synchronous operating regimes has been carried out.

The double-way feed machine (DFM) oriented oscillating electric drives' synthesis, the choice of a rational control structure and its options providing maximal operating speed and the pre-set coordinate accuracy are not possible without the estimation of transient processes taking place within the system. Even in the mode of sustained oscillations the actuating motor performs a peculiar periodic reverse operation which is equivalent of a quasi-stationary process. At the start, perturbation actions control, stop and reclose there appear additional transients in the electrical machine, which, together with periodic steady-state values, form complex magneto-electric and electromechanical couplings.

One of the most efficient instruments to investigate the transients in electrical machines at the periodic motion is the use of numerical differentiation, the availabilities of interesting to us results expanding essentially

$$U_{os}(t) = U_m \cdot \alpha_1 \sin(\omega_1 t + \alpha); U_{\beta s}(t) = U_m \cdot \alpha_2 \sin(\omega_2 t + \beta);$$

$$U_{dr}(t) = U_m \cdot \alpha_3 \sin(\omega_1 t + \alpha); U_{qr}(t) = U_m \cdot \alpha_4 \sin(\omega_2 t + \beta),$$

Ъ

where α_i – are the coefficients of signals; $\alpha, \beta, \omega_1, \omega_2$ – starting phases and voltage frequencies across the motor windings; $i = 1, 2, 3, 4$. If only the inertial load component is considered, then at different frequency feed the transient current characteristics $I = f(t)$ (1) of the moments $M_{\text{эм}} = f(t)$ (2), speeds $\omega = f(t)$ (3), and also the motors' moving elements' joint coordinate $\chi = f(t)$ (4) at starting into the DFM mode ($\alpha_1 = \alpha_2 = 1; \alpha_3 = \alpha_4 \neq 0$) or into the mode of an asynchronous motor (AM) ($\alpha_1 = \alpha_2 = 1; \alpha_3 = \alpha_4 = 0$) will have a quality format represented in the picture 1.

when considering both linear and nonlinear mathematical models of actuating motors. The numerical methods of computation allow attaining the minimum of hypothesis and getting the maximal adequacy to real processes taking place in electromechanical energy converters [1].

For the DFM oscillatory operation conditions the numerical differentiation is reasonable to be carried out according to differential system of equations recorded for flux linkage within the intrinsic frame of reference supplemented with algebraic equations for line currents, and the calculation data are to be considered in terms of the corresponding graphic charts determining the dependence of the electrical machine features, loading and feed elements effect on the oscillating system's dynamic characteristics.

At different frequency supply the regulating functions for the stator and rotor motor windings can be written as

As it is seen, the starting sequence is attended by the surge currents (I_s) and torques (M_t) emergence, that is actually typical of all synchronous and asynchronous unidirectional motion machines. However, for the DFM oscillatory operation conditions the transient is primarily of oscillation nature, the quality of which depends on the actuating motor type. In the current curves the amplitude modulation with the motor oscillation frequency $\Omega = \omega_1 - \omega_2$, and in the moment-speed curves – vibrations and surging, are observed.

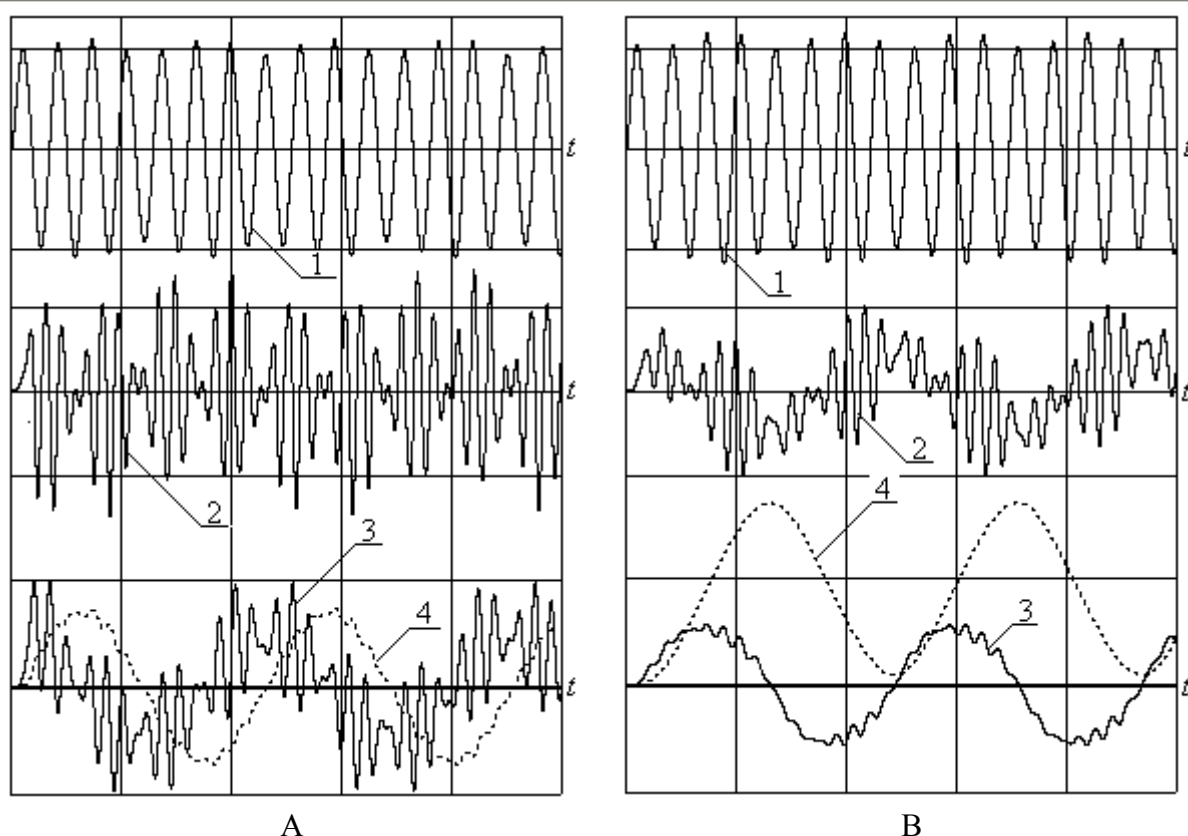


Figure 1. Time dependences of currents, torques, speed and coordinate in the DFM a) and AM; b) modes.

The fact that the motor moving element's steady-state coordinate value has a geometric displacement of the oscillation neutral point at the electrical machine operating in the mode of asynchronous motor ($\alpha_3 = \alpha_4 = 0$), while the displacement in the DFM mode is lacking, comes under notice. This fact is explained by the positional component presence in the oscillation electromagnetic DFM torque caused by the flux linkage resultant vector modulation on the move of the motor moving element [2].

It is evident that at research investigations the emphasis is made on the predetermined dynamic behavior oscillating system synthesis taking into account the parameters of the electrical machine used. As varied parameters it is recommended to choose relative values of the armature stator (R_s) and rotor (R_r) resistances, leakage inductance of stator $L_{\sigma s}$ and rotor $L_{\sigma r}$ coils and mutual inductance M .

As it is seen from the investigation the surge current I_s value behavior graphs are characterized by linear or almost linear dependences (nonlinearity doesn't exceed 10%) at stator and rotor leakage inductances change within the limits of 25%. At that the values of impact torques M_s can low for the AM mode by 30%, and for the DFM one – by 40%. Comparing the stator and rotor coils leakage inductance parameters effects on the electromechanical transients' characteristics, the identity of the last ones should be noticed once more, but still pointed at a greater efficiency of the $L_{\sigma r}$ influence from the position of the I_s and M_t values widest variation range achieving.

A brand new look the transient characteristics acquire at mutual induction coefficient M changes. So, the impact torques values increase with the coefficient M increase. However, the AM and DFM modes M_t value increase is comparable. In its turn, the mutual

flux increase affects the electromagnetic field empowerment on the secondary motor element, and it leads to the surge currents value decrease.

Another important index of electromechanical energy converters operating in special modes is the response time τ_r . At different frequency supply of the actuating motor it is hardly ever changes and the dependences $\tau_r = f(L_{\sigma s})$; $\tau_n = f(L_{\sigma r})$ bear almost linear character throughout the whole parameters variation range.

The armature stator and rotor resistances prove themselves quite opposite. Thus, with the R_s decrease the electromagnetic processes decay time increase is observed, that, in its turn, influences greatly on the period of electromechanical transients. This af-

firmation is related, in the first instance, to the DFM, for which a more obvious inductive reactance effect predominance is indicative at the R_s decrease.

As an illustration of the point, the transient quality indexes' quantitative assessment for the boundary and nominal values of the varied parameters is represented in Table 1.

The research testified that at comparable M_t values of the asynchronous motor and double-way feed machine, the last has a double excess of the steady-state torque amplitude value. The given affirmation is true for all the cases considered earlier and is typical when comparing the machines with a squirrel-cage induction and phase-wound rotor motor.

Table 1. The transient quality indexes' quantitative assessment for the boundary and nominal values of the varied parameters is represented

Transient quality indexes		R_s , o.e.			R_r , o.e.		
		0,03	0,06	0,09	0,047	0,094	1,141
AM	I_s , o.e.	2,2	2,0	1,83	2,27	2,0	1,86
	M_s , o.e.	0,23	0,6	0,5	0,5	0,48	0,646
	τ_n , c	0,1	0,1	0,1	0,1	0,1	0,1
DFM	I_s , o.e.	1,26	1,16	1,03	1,3	1,16	1,06
	M_t , o.e.	0,675	0,516	0,5	0,533	0,566	0,61
	τ_n , c	0,55	0,5	0,41	0,55	0,5	0,41

Allowing for the DFM air-gap irregularity the $\tau_n=f(L_{\sigma s}, L_{\sigma r})$ function's linearity distortion is observed. The more the design parameter deviation from its nominal value is, the more significantly the response time τ_n increases, and, in a range of cases, the oscillatory motion electric motor can loose its transient stability. The last manifests itself as the oscillation law breaking, and particularly, realization of rotation-vibration or stepwise operation, or the electric motor output shaft rotation with Ω creep speed. The own mutual inductance modulation doesn't influence significantly the other transient quality indexes (I_s , M_t), however, an error caused by engineering designs can reach in some cases 30%.

For a series of oscillation electric drives the oscillating system dynamics evaluation is of special value at the load parameters variation. In general, the complex load coefficient $Z_{mech}(\Omega)$ is frequency-dependent, it predetermining the general form of amplitude-frequency responses of the motors operating in the DFM and AM modes (Fig. 1) and, thus, the drive's transient indexes. Even moderate positional load implementation C_{mech}^{-1} leads to the AFR change and also surge current and moment values relative to the characteristics represented in the Fig. 1.

At $C_{mech}^{-1} \neq 0$ near the electromechanical resonance a sharp increase of both response time and impact torque amplitude is observed.

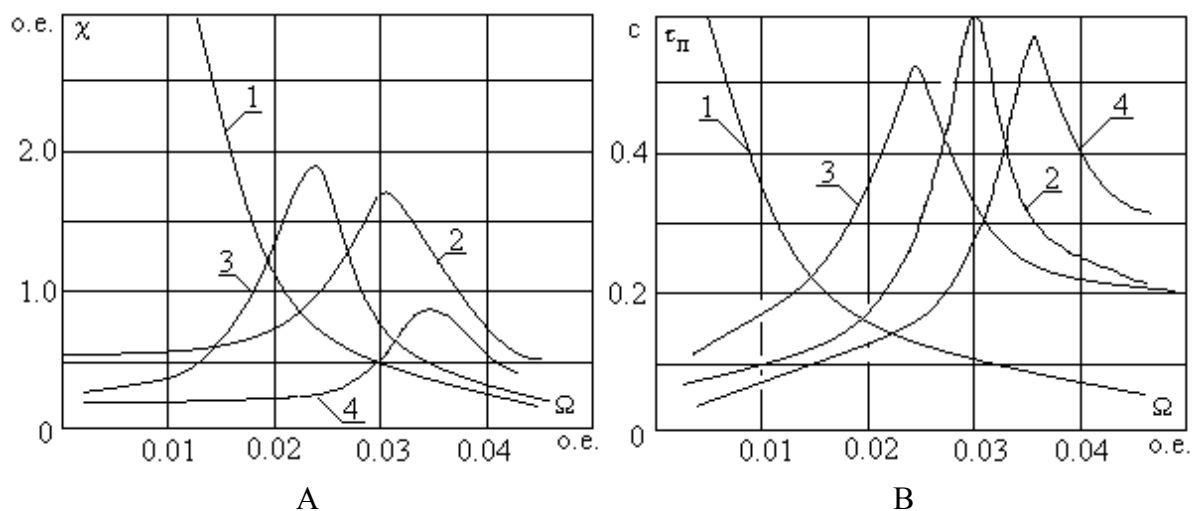


Figure 2. Amplitude-frequency responses a) and response time b) for the AM (1,2) and DFM (3,4) modes at $C_{mech}^{-1} = 0$ (1, 3); $C_{mech}^{-1} \neq 0$ (2,4).

When analyzing the transient performance in below- or above-resonance areas, the positional load, as well as inertial one L_{mech} , doesn't have any significant influence on the behavior of the dependences $I_{surge} = f(C_{mech}^{-1}, L_{mech})$, $M_{surge} = f(C_{mech}^{-1}, L_{mech})$, $\tau_n = f(C_{mech}^{-1}, L_{mech})$. However, it should be noted that the rotating masses increase fairly affects the DFM moving element generalized speed format quality. At the L_{mech} increase the carrying high frequency fluctuations and the impacts in the speed performance curve are essentially smoothed, that is attained by means of the response time double increase.

A significant influence on the transient indexes of periodic motion machines is made

by the damped load R_{mech} . Though its amount doesn't specify the electromechanical resonance condition, but influences the oscillating complex general factor of quality, actively affecting the oscillating electromagnetic torque sinusoidal components amplitude. The R_{mech} increase essentially decreases the response time and, in case of working in the asynchronous operation, regulates the oscillation neutral deviation, the oscillation amplitude decreasing and the impact torque increasing. The comparative quantitative assessment of the load parameters influence on the transient indexes of oscillation machines are represented in Table 2.

Table 2. The comparative quantitative assessment of the load parameters influence on the transient indexes of oscillation machines are represented

Transient quality indexes		L_{mech} , o.e.		C_{mech}^{-1} , o.e.		R_{mech} , o.e.	
		0,6	1,4	0,6	1,4	0,6	1,4
AM	I_s , o.e.	1,88	2,0	2,0	2,0	2,0	2,0
	M_t , o.e.	0,59	0,629	0,627	0,64	0,61	0,61
	τ_n , o.e.	0,14	0,2	0,25	0,52	0,14	0,12
DFM	I_s , o.e.	1,15	1,12	1,02	1,12	1,12	1,12
	M_t , o.e.	0,56	0,58	0,5	0,42	0,54	0,64
	τ_n , o.e.	0,28	0,56	0,25	0,12	0,7	0,3

The payroll results analysis testifies that, exclusive of the response time, the transient indexes of electrical machines when operating in the DFM mode are notably higher than asynchronous operating regimes ($\alpha_3 = \alpha_4 = 0$). However, this very index in a DFM can be considerably improved as well due to the positional load implementation.

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*Materials of conference***INTERACTION BETWEEN COMPONENTS AT METAL COMPOSITES PRODUCTION**

Klyuchnikova N.V.

Belgorod State Technology University named after Shukhov V.G., Belgorod, Russia

An effective combination of metallic and non-metallic components of various composition in particular proportions offers an opportunity for finished materials' physical-mechanical and radioprotective properties' change in the proper direction. As a non-metallic component large grains and fine grades of rocks and minerals, glass and ceramics industries' wastes are used. One of the most important problems of chemistry and technology of metal composites is the problem of bond character and adhesion power between the components. The bonding between the phases in heterogeneous systems is determined by the ratio of surface energies, surface-tension value between the phases and is carried out both by means of Van der Waals' forces and carrier compounds and solid solutions formation. For the estimation of a possible interaction between the phases in metal composites it is admitted to consider the characterized by the limiting wetting angle wetting between the components. A good wetting of metal-like carbides and nitrides by refractory metals compared to the wetting of fire-resistant oxides by them is explained by the metallic bonding in the lattice of these compounds, their inclination to form solutions with metals and exchange reactions between them.

Thus, considering wetting as the main precondition for the formation of a solid structure, all metal composites should be divided into two main groups:

- 1) metal composites, wherein the non-metallic phase is wetted by a molten metal well;
- 2) metal composites, wherein the wetting of a non-metallic phase by a molten metal is not too much [1].

The composites of metal-bond metal-like refractory compounds, i.e. most carbides and silicides having the interstitial alloy structure and also borides and silicides, are referred to the first group. Due to its good wetting by molten metals a tight and stable bond between the metal and metal-like phase is typical of the metal composites of this type. Such metal composites sinter at the temperature that is a little higher than that of binder metal melting point. The formed at that fluid metal phase wets the surface of the metal-like compound searching into the finest cracks and its grains' surface irregularities and providing thus the highest strength of the composite. At that, the formation of some carrier compounds and subsolution is possible.

The second group combines metal composites on the base of oxides. The last ones are wetted by the molten metals not properly, hence, to reach a stable

bond between the metal and non-metallic component is not possible, as a rule. For this reason at sintering of metal composites of the oxide – metal compositions at the temperature exceeding the binder metal melting point the metal runout occurs. To avoid such a phenomenon the metal composites of the oxide type are burnt at the temperatures, which are lower than those of the metal's melting point, at which the metal is in a plastic, but still solid state.

For the wetting quality improvement between refractory metals and high refractory oxides in the process of metal composites' sintering the oxides should have a high-surface area. Sometimes the oxides forming together with the basic one the solution phase are introduced into the metal ceramic composition. The additions of its oxide are made to the metal, if this oxide can interact with the basic one of the system. The alloying additions are made to the basic metal; at that, the alloying metal should be an oxygen hungry one, that promotes the oxide's wetting by the alloy being formed.

The oxide oriented metal composite will be strong and tight when the metal and non-metallic component form an intermediate layer connecting both phases. Such an ideal case is the introduced oxide and binder metal one solid-solution formation, for example, cermet of the corundum – chrome composition.

To a certain extent the properties of metal composites are determined by a range of physical-chemical processes taking course when heated:

- 1) wetting of the ceramic phase by the metal;
- 2) chemical interaction of the phases;
- 3) mutual solubility of the phases [1].

The properties of metal composites can be changed when choosing different metal-non-metallic components relations, that is easy to achieve by powder technique practice.

When melting during the burning-in, the metal particles of the metal composite act as a binder wetting and connecting the grains of the other component or making a chemical compound with it. As the result of their interaction new materials possessing specific properties and not being simply a sum of metal's and non-metallic component's properties appear [2].

For the time being the formulation of metal composites is to a large extent selected empirically, but still there are some theoretical preconditions. The determinative factor in the binding material choice is its ability to wet the non-metallic component. The wetting can be attended in the metal composite by a chemical change between the components (they are the phases as well) with the formation of a new phase in the form of a new compound or a solid solution. The better the wetting, the higher the quality of the metal composite obtained.

In the sphere of obtaining composite materials high temperatures most of the components are thermodynamically nonequilibrium ones, able to undergo different reactions with each other at the phase boundary. Physical-chemical phenomena taking course on the components' boundary surface are rather complex and nowadays studied not well enough. Generally, the accumulation of experimental data on the interaction between the most advanced metals (aluminum, magnesium, nickel, titanium and some others) and fibers – boracic, carbon, glass. But it should be noted that nowadays there is some calm in composite materials studying, and the top of the investigations falls on 70-80s when the majority of the data were got and some theoretical developments were started both in our country and abroad.

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DATA PROCESSING SYSTEM RELIABILITY ANALYSIS BY NETS WITH WINDOWS VISTA OPERATING SYSTEM CONTROLLED COMPUTERS

Kovalev A.S.

Orel State Agrarian University, Orel, Russia

The computer network reliability is assured by the whole system of hardware and software tools providing concurrent processing of various privacy information by a user group without access violation. It is especially typical of the Windows Vista operating system, which has an entirely reworked network architecture called to simplify and enhance operational reliability in the net with the help of Vista maximally.

The Windows Vista controlled correctly set network usually works without failures, but problems and errors still spring up. For their detection in the Vista system there are diagnostic aids. The primary diagnostics is performed in the “Network management and public access center” window and in the viewer of the full size net card. If there are network connect problems there will be corresponding graphic symbols. The receiving of more accurate information about the network connection state is seen in the “Network connection state” window, where the key connection parameters IPv4, IPv6, data processing

rate are specified, and in the network operation run-time the number of sent and accepted bytes is fixed.

In the “Network connection data” window current values of the TCP/IP key parameters are viewed. When data reduction error rising, the troubleshooting procedure is fired. This program's operating results are reflected in the “Network diagnosis” window, where the list of problems is seen and recommendations on their correction are presented.

The connection ensuring can be executed by the “ping” command. This command lets validate the availability of connections with another computer on its name or IP-address. This is the primary network connection diagnosis asset. The “ping” command causes sending special packets to another computer, which, having got them, sends them back. The packet transit time and message about the packets' being lost is shown in the screen. The connections with a local area network computer and the Internet are controlled by the “ping” command.

The “ping localhost” command sends packets “to itself”, that allows checking the TCP/IP work on the local computer. The transit time should be less than 1 msec.

In the “Task manager” window, “Net” tab, the control over the network adapters' work is carried out. There is a list of network connections and their activity graphs, which define the net use intensity and its zero error capacity, here. The detailed analysis of the net adapter work presents more than twenty additional net parameters. The “ipconfig” command reflects the TCP/IP work parameters.

The “tracert” command allows tracing the path from one site to another and detecting the place, where the connection break occurred. In solving complex data processing reliability problems in the network the Windows Vista help system can explain rather extensively and deeply.

The available firewall provides protection from an unauthorized intrusion into the computer network. The firewall is realized both by hardware and software, performing the role of unauthorized users' attempt avoidance to get the access to the connected with the Internet private IP network – especially the intranet. All the messages, which don't meet the specified security criteria, coming from or entering the intranet, are stopped by the firewall. The internetwork security methods including the packet filters and application gateways are a reliable barrier for illegal requests.

The reliability is generally associated with the ideas of stability and system operational safety. It is measured as the function of time taken between failures and is denoted by the term of “Meantime between failures” (MTBF). The database integrity and the possibility of warning about the expected hardware failures are the other two reliability aspects. The SMART (Self-Monitoring, Analysis and Reporting Technology) and RAID systems guarantee the work continuity

and data safety even in the fault case. When loading, the memory self-testing, during which the system of memory error checking and correction (ECC) allows improving the data integrity, should be referred to the reliability augmentation means.

In the wireless local area network media the reliability is influenced, as a rule, by the quality of connection with the remote computer connected in the Internet with the hot spot. There appears a problem in the configuration of connection with the Wide-Area Network in the hot DHCP and NAT spots and in the correctness of binding IP-addresses to the devices, and also the correctness of their conversion into an integrated IP-address used for the connection to the network and for the outlet to the interface of the wire-connected network. Finally the networks aim to achieve the reliability of 99,999%.

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RESEARCH OF AN OPPORTUNITY OF USE POLYMERIC MATERIALS IN DISPOSABLE CONSTRUCTION OF VARIOUS PROTECTIVE BARRIERS

Mironov V.V., Yakimova I.V.

The state architecturally-building university, The state oil-and-gas university, Tyumen, Russia

Annually in this or that part of the world, including Russia, flooding and forest fires suddenly occur, caused by the various reasons, which cause huge damage the natural and the population. Existing ways of protection against these acts of nature not always lead to desirable result. First of all, it is caused by imperfection of means on struggle against elements. One of major factors of successful struggle against sudden flooding and duly localization of forest fires is time of a construction of protective barriers, such as temporary water-retaining dams and fire-prevention protective contours. Existing technical decisions of similar purpose are expensive enough and labour-consuming at their realization besides demand significant time for a construction of protective designs in extreme situations.

We have investigated an opportunity of use of a light, inexpensive polymeric packing material, which is serially let out by the domestic industry practically in each large city of Russia, in disposable designs of an extreme construction of protective barriers from sudden flooding and for localization of local forest fires, and also emergency spreading burning liquid hydrocarbons. Ways of a construction of various purpose protective barriers which are used in designs of the water-filled polymeric casings are patented in the Russian Federation. Realization of these ways in prac-

tice will allow to reduce considerably expenses and time of a construction of protective barriers in extreme situations, it will essentially raise efficiency of struggle against acts of nature, such as sudden flooding and forest fires, and also will raise efficiency of liquidation consequences of technogenic failures.

Working capacity of temporary water-retaining dam constructions made of water-filled polymeric casings and contours of protective barriers for localization local forest fires, and also emergency spreading burning liquid hydrocarbons, made of the permeable water-filled polymeric casings has been checked up experimentally on full-scale fragments and has yielded encouraging results.

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TRIFOCAL DIFFRACTIVE-REFRACTIVE INTRAOCULAR LENS – FIRST RESULTS

¹Cherednick V.I., ²Treushnikov V.M.

¹State University, ²"Reper-NN" enterprise, Nizhny Novgorod, Russia

The natural human eye-lens makes possible to see sharply at any distance within the diapason from the infinity to 20-25 cm on account of accommodation – that is the curvature change of its refractors. An artificial crystalline humor (intraocular lens), implanted instead of the one lost its transparence because of the natural eye-lens's cataract, cannot provide such a possibility so far. In an elementary variant an intraocular lens represents a monofocal lens performing a sharp image of objects located in a certain fixed distance in the retina. It is usually either at a short distance (book reading) or far – electively. For seeing at other distances the eyeglass correction is needed. For partial compensation of this disadvantage nowadays more constructively complex (and, naturally, more expensive) bifocal intraocular lenses, making possible to see sharply at all distances, are produced and implanted. Both refractive lenses, forming the image in accordance to the laws of geometric optics, and diffractive-refractive ones, in which the focusing with the help of a diffractive relief in one of the lens's surfaces in combination with the refraction in the other one is used for the image formation, can be bifocal. In the first instance the bifocality is achieved either on account of various curvature of the refractive surfaces or on account of the refraction factors' diversity at various radial distances from the lens's center. In the second instance the bifocality is achieved on account of the fact that there can be several diffraction maximums promoting a sharp image. The sample of the bifocal refractive intraocular lens is the "Gradiol" lens

produced by the “Reper-NN” Research and Development Enterprise (Nizhny Novgorod, the co-design with the SE IMTC “Eye Microsurgery” named after the Academician S.N.Fyodorov, Moscow). There is one more lens of a less diameter with another refraction factor, with another curvature of the refractive surfaces and with another (less) thickness index inside the central part of this lens. The samples of a bifocal diffractive-refractive lens are the ReSTOR lens of the firm “Alcon”, the “Accord” lens produced by the “Reper-NN” Research and Development Enterprise (the co-design with the Institute of Automation and Electrometry SB RAS, Novosibirsk) and the “Record-2” lens also produced by the “Reper-NN” Research and Development Enterprise (the co-design with the Nizhny Novgorod State University named after N.I. Lobachevsky). The main difference of refractive and diffractive-refractive lenses lies in the fact that in the first instance at bright lighting and, respectively, at a small diameter of the pupil the peripheral part of the lens can happen to be fully closed and the corresponding focus will not be realized – the lens will become a monofocal one. In the second instance the lens remains bifocal at any papillary diameter.

There is a ring diffractive relief, providing the diffraction maximums performing the images in the retina, in one of the surfaces (usually plane) of the diffractive-refractive lenses. The second surface (usually spherical) remains smooth and provides an extra refracting power, enabling an opportunity to run out at a considerably less number of diffractive rings, than if the second surface were also plane (retarder). The diffractive relief profile can be rectangular (binary construction), triangular or of any other, more complex form, for example, sinusoidal. The diffractive-refractive lenses produced nowadays all over the world have got the triangular profile. The triangular profile preferability is conditioned by the fact that at such a form of the profile the intensity of light energy in the diffraction maximums is close to its theoretical limit. The abovementioned ReSTOR and “Accord” lenses are the ones with the triangular profile. In the ReSTOR lenses the relief depth apodization is applied – the relief depth reduces with the removal from the lens center along its radius. The light energy distribution between the diffraction maximums (foci) depends on the relief depth. The less the depth - the less energy falls on the maximum of the first order corresponding to the near sight, and the more energy falls on the maximum of the zero order corresponding to the distant sight. At bright day lighting and small papillary diameter the ReSTOR lens provides an approximately equal distribution of the light energy between both maximums, and in conditions of poor lighting almost all the energy falls on the maximum of the zero order, i.e. at poor lighting this lens transforms actually into a monofocal one corresponding to a distant sight. In the opinion of the authors of this working there is no necessity to see the near located objects in the twilight.

The bifocal lenses of any design afford an opportunity to see equally well both at a distance (from about 12-15 m and farther) and near (25-40 cm). But the image of the objects disposed at the between distances remains misfocused. We don't speak about the total sight or orientation ability loss, but one has to watch TV, for example, in glasses. To provide the sharp sight at the between distances a third focus is necessary. The corresponding trifocal lenses can be refractive and diffractive-refractive as well. In the first instance a further technology complication and, respectively, cost increase are inevitable. In the second instance the technology doesn't complicate, but even simplifies. As it was noted earlier, all the world's producers of diffractive-refractive lenses use a diffractive relief with a triangular profile. Such profile gage making requires a rather complex technology and high precision modern equipment, that conditions an extremely high cost of such lenses (up to thousands of dollars). A diffractive relief with a rectangular profile is considerably easier to make. Only a ring gage, which can easily be made on an electron-beam lithography installation, is necessary. As it was already noted, the intensity of diffractive maximums for a triangular profile is impossible to excel. The corresponding intensity for a rectangular profile can be lower by 20-40%. It is unlikely that such intensity reduction will represent a serious impediment for anybody. It is common knowledge that the human eye retina easily accustoms to the illumination intensity changes from 10^{-6} to 10^5 lx. The intensity variation by tens of per cent and even many times against such a diapason represents an insignificant value. A person will take no notice of such a change, but will notice the artificial eye-lens cost variation many times.

There is one more highly serious circumstance saying for a rectangular profile. The computer modeling shows that a diffractive relief with a rectangular (and sinusoidal) profile gives three diffraction maximums suited for the image formation – minus one, zero and plus one orders. The rest maximums of higher orders have got a negligible intensity and are useless for practical application. Thus, a diffractive-refractive lens with a rectangular profile refractive relief can be used both as a bifocal intraocular lens and as a trifocal one without any structural and technological changes. In the bifocal variant only two maximums of the three available ones are simply used, and in the trifocal variant all the three maximums are in use. Both variants differ only in ring diameters and groove depth. The computer modeling also shows that the diffractive relief with a triangular profile gives only two diffractive maximums suited for the image formation – zero and plus one orders. The third maximum is principally impossible to obtain with the help of a triangular profile construction; the lenses with such a profile cannot be trifocal by all means. For the illumination intensity increase in the rest two maximums one has to pay with the third one loss – the

energy conservation law is impossible to avoid. The intensity variation can be compensated by an adequate sensitivity shift of the retina, and the third maximum loss cannot be compensated at all.

At the present time, the "Reper-NN" Research and Development Enterprise – is the only one of the kind, which produces trifocal diffractive-refractive intraocular lenses "Record-3" with a rectangular profile diffractive relief (the lenses "Record-2" are a bifocal variant of the same design). These lenses are a co-design of the Nizhny Novgorod State University named after N.I. Lobachevsky (computer modeling and concrete construction calculation) and the "Reper-NN" Research and Development Enterprise (fabrication method and production). The first clinical trials of the "Record-2" lenses and the world's first successful clinical trials of trifocal lenses ("Record-3") have been carried out in the Cheboksary Branch of the FSU IMTC "Eye Microsurgery" named after the Academician S.N.Fyodorov [1]. The results of these trials (about a hundred patients) testify that the patients with a bifocal eye-lens "Record-2" see equally well both nearby and distantly, and the patients with a trifocal eye-lens "Record-3" see equally well nearby, distantly and in between intervals. The area of the distances corresponding to a poor image focus has significantly decreased. The questionnaire survey of the patients has proved their satisfaction with the surgery results – a person with a trifocal intraocular lens has got an opportunity to see well distantly (to drive a car), read a book and watch TV without glasses on.

Therefore, a trifocal intraocular lens, principally exceeding all the existing bifocal lenses in its functional characteristics, has been calculated, designed and for the first time in the world manufactured on the "Reper-NN" shop floor in collaboration with the

Nizhny Novgorod State University named after N.I. Lobachevsky. There is no trifocal lens efficient analogue in the world for the time being. The lens has successfully passed the first clinical trials.

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PEA PLANTS' SUBSTRATE HEAVY METALS CUMULATION RESISTANCE PROMOTION BY MEANS OF SEEDS TREATMENT WITH SUPER-LOW DOSAGE OF SALICYLIC ACID

Shalimova O.A., Shtakhova T.A.

Orel State Agrarian University, Orel, Russia

The investigations of heavy metals content (Pb, Ni, Cd) in pea plants with the pre-treatment of the seeds with salicylic acid has been carried out. The induced plants' growth in the media rich in heavy metals has been investigated. It has been established that the treated plants accumulate toxic compounds in a less degree compared to the control and retain the ability to healthy growth in polluted media. It is offered to treat the seeds with salicylic acid in the concentration of $2 \cdot 10^{-8}$ M before planting.

Table 1. Heavy metals content in plants and MCL for their vegetable forages.

Substance	HM content in plants, mg/kg				MCL in vegetable forages of natural humidity, mg/kg
	Non-treated with SA		Treated with SA		
	смесь Кноппа	Knop's mixture + Pb, Hg, Cd	Knop's mixture	Knop's mixture + Pb, Hg, Cd	
Cadmium	<0,004	0,42	<0,004	0,10	0,3
Lead	<0,012	8,52	<0,012	2,26	5,0
Nickel	0,058	12,32	0,058	1,17	3,0

Cultivated plants intensively absorb special substances from the soil solution. The pea family plants can accumulate a considerable amount of metals, the dangerous for animal bodies heavy metals (HM) (with the density of 5 g/cm^3) among them. Taking into account a regular increase of not used in the metabolic process substances' concentration, a health hazard for people or animals making use of such contaminated products can emerge in the following food links [2].

In connection with the abovementioned the laboratory research on the study of physiological growth

and the ability to toxic metals accumulation by the pea plants' organs at the pre-sowing treatment of the seeds with salicylic acid (SA) with the concentration of $2 \cdot 10^{-8}$ M [1] was carried out. The investigations of heavy metals' - Pb, Ni, Cd - content were carried out in the accredited by the scientific research testing laboratory of the Orel State Agrarian University according to standard practice [3]. The valuation of the physiological state of the plants was performed visually. For the heavy metal standard the limits of their concentrations promoting normal regulation of functions in plants are taken.



Pic. Development of pea plants against the background of heavy metals:
1 – non-treated with SA; 2 – treated with SA.

The studied plants varied in their ability to accumulate heavy metals. At the pre-treatment with SA the toxic metals accumulation in the quantities not exceeding the MCL (maximum concentration limit) was registered in the tissues. At that nickel was accumulated in the maximal concentrations, and cadmium – in the minimal ones. In the nutrient solution with a high concentration of HM the non-treated plants accumulated the metals in the concentrations considerably exceeding the MCL. The data of the table show that the lead content in this variant exceeded the norm 1,7 times, and nickel – 4,1 times. As the results of visual observations testify, a high HM concentration in the nutrient mixture without the plants' pre-stimulation with super-low SA dosages leads to the inhibition of growth processes (pic.).

According to the analysis results the plants grow better and accumulate a less amount of HM when using super-low dosages of endogenous stimulants of nonspecific resistance, which salicylic acid is referred to. This method allows obtaining the envi-

ronmentally sound forage crop at a high technogenous load.

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Shot report

USE PERSPECTIVES OF MULTIFUNCTIONAL SPACE SYSTEM OF RUSSIAN-BELARUSIAN FEDERAL STATE FOR HUMAN PURPOSE

Menshikov V.A., Pushkarsky S.V.,
Lysy S.R., Menshikov V.V.

*Development and Research Institute of Space Systems
named after Maksimov A.A, Moscow, Russia*

The article is devoted to the possibilities of perspective multifunctional space system of the federal state of Russia and Belarus to the benefit of maintenance support of Russian and Belarusian specialists' education, training and retraining process. Both general problems connected with the Federal State multi-

functional space system creation and the problems of its application for human purposes, in the interest of Russian and Belarusian citizens' training using a distant mode of study in particular, have been considered in the article.

In the modern stage of the Federal State development an effective economic cohesion of Belarus and Russia is impossible without the creation of an integrated information and educational space affording an opportunity to get and apply the data throughout the whole collaboration spectrum operatively. Taking into account the current level of the space systems and technologies development one can legally speak nowadays on the paramount role, which the space-

system engineering is called to play in the formation of such space.

For the Federal State the application of space means is of singular value. The specific character of its geographical position, resources and socio-economic objects' allocation is such that the majority of socio-economic programs cannot be successfully implemented without using the results of space activities. The space collaboration of the two countries goes beyond the scope of carrying out joint research. The agreements on integration and joint use of space means by Russia and Belarus in such directions as rational use of nature, navigation and telecommunication development, carrying out the earth surface ecological monitoring, effective use of transport and hydrometeorologic forecasting enhancement, teaching, training and retraining of personnel.

The creation of a multifunctional space system of the Federal State will promote the integration processes' speed-up in the Federal State in the field of space activities to the benefit of an integrated information and educational space creation, the efficiency upgrading of spin-off benefits from space research in socio-economic, ecological and humanitarian spheres.

The main problems being solved while creating the multifunctional space system of the Federal State are:

- the introduction of science intensive space technologies into different science, engineering and economics realms inside of the confederacy of Belarus and Russia, their joint market promotion of space technologies and services;
- the creation of stable cooperation of rocket-and-space branch organizations of Belarus and Russia on the development of perspective space means and technologies including micro- and nanotechnologies;
- the development of organization basis and regulatory framework for the Federal State's multifunctional space system effective use to the benefit of the Federal State's regulatory body information support;
- the Information Analysis Centers structures creation to the benefit of the Federal State's regulatory body decision making provision in daily activities and in conditions of emergency situations on the ground of complex monitoring information use;
- the Federal State's consumers' provision with navigational data got by the space navigational systems on behalf of solution of wide range of socio-economic problems, the freight traffic activity efficiency upgrading and high precision positioning among them;
- training and retraining of the Federal State's specialists in various realms of science and engineering, in the field of space activities using distant mode of study as well;
- the international cooperation with the Third Countries in the field of creation and joint use of the Federal State's multifunctional space system.

The main application areas of the Federal State's multifunctional system are:

- the provision of Belarusian and Russian consumers with monitoring information;
 - the provision of high precision positioning of static and mobile objects, mobile facilities monitoring and control in the Federal State's territory and abroad;
 - the enhancement of possibilities to get education by the citizens of Belarus and Russia living far from large education centers.
- In general the multifunctional space system of the Federal State represents a complex managerial and engineering structure including the existing and being created (based on new generation micro-satellites) orbital technologies and also a special earth based complex including:
- the system of consumers' provision with monitoring information;
 - the interstate navigational information system;
 - the distance education system.

It should be noted that the maintenance logistics problems of the educational process using modern telecommunication technologies, the space one among them, in the Federal State's multifunctional space system are given special priority. It is associated, first of all, with the fact that education is the base for any economy branch development in any country, and modern space technologies open manifold possibilities for getting necessary knowledge even in the most hard-to-reach and remote from education centers aggregations.

When speaking of the Federal State, the steady growth of joint scientific and technical programs and projects increases the demand for highly qualified young specialists and scientists. However, the practice testifies to a difficult enough personnel situation in scientific organizations and on the industrial shop floors of Russia and Belarus, which is conditioned by the lack of proper inflow of newcomers and, as a consequence, personnel "aging" of a variety of both countries' industry sectors. Thus, for example, the research carried out at principle enterprises of Russian space branch shows that the average age of specialists is 48 ÷ 50 years old, in Belarus - 45 ÷ 46 years old accordingly, while the most efficient and inventively active phase of human activity falls on the age period of 25 ÷ 45 years old.

Under these conditions the Russian-Belarusian education and knowledge dissemination system creation within the multifunctional space system framework is becoming an extremely important, topical and long-run objective.

One of powerful instruments to use in such a system for educating, training and retraining specialists is distance education obtaining in the latter days more and more prevalence.

The distance education is called to solve a considerable part of the problems, which have assumed a

global character in the present-day socio-economic environment since the traditional forms of getting education and learning models cannot meet the demands for educational services usually focused in large cities or education centers and getting quickly renewed modern special knowledge which is owned by a limited number of specialists.

With due account for the abovementioned and keeping in mind the perspective of such a mode of study and specialists' training within the framework of the Federal State's multifunctional system for the purpose of the distance education process maintenance support, training and retraining of specialists on polytechnical and humanitarian specialties in the territory of the Russian Federation and the Republic of Belarus, it is offered to create a special earth based complex of the distance education system.

The special earth based complex of the distance education system is destined for:

- the provision of carrying out video-sessions (video-lectures, video-seminars, video-consultations) on the real time basis;
- the provision of telelectures delivery inclusive of the ones on the real time basis with audio-feedback;
- the provision of e-learning organization using textual, audio-visual and multimedia teaching aids both in off-line and on-line modes;
- the provision of off- and on-line testing and knowledge assessment;
- the delivery of audio- and video-information in the direction from the teacher to one student or a group of learners allocated in different educational institutions of Russia and Belarus in simplex mode and duplex (interactive) one with answers to questions (audio- and video-conferences);
- the provision of carrying out experiments from remote laboratories and performing academic assignments on models, mathematical programs using databases of the distance education technical centers;
- the provision of digital information arrays (electronic text-books, reference books, methodical literature, tests, appraisals, etc.), audio- and video records, slides, etc. mapping onto the means of collective and individual user;
- the provision of gathering, processing and keeping all the information necessary for educating;
- the provision of an interactive access to the distributed database;
- the provision of video-lectures creation, electronic educational aids and courses development;
- the provision of information security from virus onslaughts and unauthorized data alteration attempts, database integrity control, non-admission of paid information playback without payment, accounting and control of information payment.

For the achievement of the stated objective and the abovementioned problems solution a distributed network of distance education maintenance centers

and group terminal complexes and personal terminals of individual users connected with each other by earth based and satellite channels is being created in the territory of the Federal State.

The first steps in the distance education system creation have already been done both in the Russian Federation and the Republic of Belarus. Thus, in the Research and Development Institute of Space Systems named after Maksimov A.A. a distance education maintenance center has been created, the hardware components of which have provided the carrying out of academic training of specialists in ground control and connection monitoring system for the "KazSat" space system using distant mode of study including such kinds of teaching as case-technologies and video-seminars on the real time basis.

The use of distant mode of study allowed the specialists of Kazakhstan to get quality basic academic knowledge on the ground control and "KazSat" space system connection monitoring system, that has become the foundation for their successful practical training and work on staff facilities. Thereat the economic benefit made ~ 30% from the forecast expenditures at the traditional form of academic education (about \$120 000).

Within the structure of the Belarus State University the Aerospace Education Center has been formed for the space activities area specialists training and retraining coordination. In the network of this Center the educational technologies (inclusive of the distance education ones) of personnel training in the branches associated with accepting, processing and practical use of the Earth remote-sensed data, including the total cycle from the space information reception to the topical data obtaining, are developed and approved.

Finally it should be noted that the distance education system creation within the framework of the Federal State multifunctional space system has got important perspectives and it is connected with its use effect lying in:

- the provision of stable Russian and Belarusian educational systems integration;
- the enhancement of getting knowledge by different categories of citizens;
- the enhancement of education contents exchange between educational institutions of Russia and Belarus;
- the provision of employees' training, retraining, educating and testing process continuity on account of distance education high technologies use;
- the advanced training of specialists without primary activity interruption;
- the new specialists' training terms reduction due to specialized education programs use;
- the terms reduction of teaching specialists new technologies;
- putting down expenditures for specialists training.

THE SCIENCE IN THE SYSTEM OF CULTURE AND CIVILIZATION

Panischev A.L.

Russian State Social University, Kursk, Russia

The article is devoted to the concept of science in its unity with the civilization. It is supposed that the very civilization, its state system have provided basics for the development of science as the independent social institution and the form of the world cognition. At the same time based on the civilization the science is setting such an impetuous rhythm of life for a person in the system of culture and civilization that now we have escalation of person adaptation problem in the conditions of all-time varying environment.

The question of time and reasons of origin of the science as independent, purposeful research action has no certain answer. There are two main points concerning the causes of the science origin. According to the one of them the science has appeared as a cause of external sociocultural conditions, practical needs of the society. The other point of view observes the origin of the science as a cause of its own immanent laws. In other words, the origin of science is considered to be autonomic.

In this article is based on the first point of view. We may admit, that science has developed independently, but its dangerous to accept for a fact that world of the science and scientific knowledge is independent on social and cultural needs of humans. In this case we use the word "must not" because once appeared the knowledge remain even after the death of civilization, which had given a birth to this knowledge. Knowledge, which has been work out by a civilization, for example Maya, after death of this civilization continues to be evidence of the ancient American people of Maya. Besides, the scientific knowledge is able to suppress and restrain a human's think, irrespective of its direction. More than that accepted science is able to show the direction of the mental work of the scientist. A. Kamu wrote, that man is a victim his ideas. He recognizes its beliefs, organizes life accordingly to its beliefs, and depends on its ideas [1, c. 243]. Speaking about autonomic origin of science one should notice the fact that in condition of its independence on the culture of social organism it can repress it. N. Berdyaev notes that, our be-

lief in the world so strong, that information about the physical world gets insistent, obligatory character, in other words, the form of knowledge [2, c. 65]. That is why, though being able to develop irrespective of the society with its own immanent laws, science shouldn't override people. On the contrary, people should have control under science knowledge.

However in this case arise the question about correlation between culture and civilization in the contest of they relation with a science. Is the origin and appearance of the science connected with culture or with civilization? To answer this question we need to examine the concepts of *culture* and *civilization*. To reveal the most significant the differences between the culture and civilization, we address to the study of N. Berdyaev. The philosopher supposes that the culture turns to the past, takes care of traditions, keeps memory about its history. The civilization has a tendency to the future, strives to innovations; the feature of civilization is the ideas of progress and linearity time [2, c. 700-701]. In accordance with N. Berdyaev views, its difficult to say that appearance of the science has the relation only with culture. There are more reasons for statement, that origin of the science has the relation with civilization. The reasons of correlation between the science and civilization will be object of this article.

Its correctly to say, that origin of the science is to be observed in the context of civilization development. First, innovations are typical for the science, this means the presence of ideas of progress and linearity time in the society. Second, objective is an important

feature of scientific knowledge. The concept *objectiveness* has relative character in the cultural and religious life of people. For instance, in faith spirit experience has individual, subjective character [3, c. 131]. The significance role play the subjective standpoints and values of the certainly clan in understanding of traditions, cultural norms. The civilization turns to the neutrality. We will try to prove this idea.

So, the present of state is the main trait of civilization. Certainly the state system lets say, that a society achieves the level of civilization. Any country is based on the positive law – the complex of juridical laws, which have objective character. The country guarantees fulfillment of the laws and provides they efficacy. Culture in contrast to civilization turns to subjective attitude. Besides, the fists resolves are bases on the traditional norms, which have the unity understanding in the environment of the only culture. However these resolves have other perceptive in the environment of other cultures. There are examples of the laws, which have been provided by strength of traditions of the regnant clan. For example, the complex of laws from the schumer town Ur (XXII age B.C.). More famous resolves Babylon king Hammurapy (1792-1750 B.C.). Though the first resolves appeared in the country of ancient Orient its impossible to say, that laws of the country of ancient Orient had been based on the principals of civilization. These laws had turned to the subjective interests of the regnant clan, which attempted to lead other clans. But the interests of the regnant clan had the different sense in views of other clans. That is the reason why the countries of ancient Orient had been subdivided in the time of heyday, unity took very little periods. On the one hand, there were many factors, which had to expedite the consolidation of people of the countries of ancient Orient, for example, the common language, religion. But, on the other hand, all countries of ancient Orient out mach effort to suppress separatism, as the law were fixed on the regnant clan interests.

For sure, the power of oriental culture could stimulate development of knowledge about physic world. Many oriental towns had become the centers of development of different fields of science. However the knowledge appeared in the atmosphere of the oriental culture are not considered to be scientific. Fist, awareness about the world had been interpreted according to the stereotypes, standpoints, norms of regnant clan. Second, religion had been substantive bases for this knowledge. At last, very few people could get the knowledge, as a rule, they were priests and state officials. To get the knowledge considered to be a privilege, the feature of a certain group of people. So, in India the brahmans could have information, which could not have other people, because any knowledge must have to correlations with dharma of social status of definite group of men.

The fist national and cultural neutral resolves is considered to be Roman law. It suggests objective, unity demands for people regardless of cultural, national, relational belongings. Every citizen of Rome had the right to be acquainted with the norms of the Roman law and to interpret it objectively. This feature of Rome civilization was the significant cause of the science origin, because neutrality is one of the treats of scientific knowledge. In this case relevancy say, that law, as discipline, is the fist real science. Law as an independent field of practical and theoretical science started its development in the ancient culture and became an important subject in the medieval universities.

So, the state having proved the law as major a principle of state life, provided rise of the science and its incorporation to the social entity.

To prove the point, that the law is the fist real science we will pay attention to the process of development of Greek philosophy. Greek philosophy followed the principle of provability; this is a significant treat of scientific knowledge. The principle of provability is interrelated with another treat of science; this is neutrality. A large role belongs to the

sophistry while developing the principle of provability. This philosophical school followed the rule that any idea must be proved and accepted by the most of people. Besides, the principle of provability was rooting in the political life of the society. So, there was a law in the legislation of Solon, according to it every citizen of policy had to take side of any party in the political life of police. The man lost the citizenship, if he didn't take part in the political life of policy and didn't take somebody's part. Therefore, every political party had to prove that its ideas were more profitable, than ideas of other parties. In such a way, the principle of provability was taking root and was supported by the government. Moreover, this principle leads to the state establishment. There the state protected principles of neutrality and provability, because it was the basis for development of justice as an essential trait of the state. At last, the principle of provability got practical meaning and at the same time got understanding as necessary conditions for the law and the state function.

There is another feature of law as science. This is the succession in the comprehended of generations. This idea has been expressed by Leonardo da Vinci, who thinks that the most useful science is that which has product, which can be clearly described to other people; and vice versa, the science is less of use, when its result can not be explained for people [4, p. 361]. The law is reflected on the paper and is interpreted regardless of cultural, religious points and the period of historical time. The modern human understands norms of Rome law, for example, as an ancient roman understood it. The Rome law's principals let it spread.

In the medieval time the law was the basis of the state existence. For sure, most of the field's science was not always real science, because they were not supported by the theory, directed on theology and the practical aims of society. However the law had both good theoretical basis and practical necessity. This necessity was observed on the different levels of social structure. Accord-

ingly there were four major kinds of the court: the court of a senior (feudal lord), the court of a towns, the court of a church, the court of a rein (state's court). Each of these courts solved the juridical problems of the different character. So, the court of a senior solved the problems in the small region, for example, in the village, which belonged to the feudal lord. The court of towns solved the problems within the certain town rage. The other two kinds of court solved the functionalities of the higher level. So, the court of rein faced the dispute between the lords. In the process of solution of a dispute between the lords a rein provided security for the most of people.

The court of rein and the court of church long time had competed with each other for a long time. From time to time their rivalry leads to the army clashes. The most hard conflict begun in 1078, continued more than 30 yeas and finished by victory of the church. As a result the court of rein remained as the main organizing part of the state life. In the following time the system state law and court of the country became more complicated. Development of the law, as a rule, was determined by practical needs, but it was based on the theory. The theoretical principals of medieval law lay in the Roman law, which was taught in the medieval universities on the faculty of law. It shows that the law of medieval states preserved the connected with the culture of ancient Rome and included the norms of antique world. That is why we can say, that positive law, based on the state resolve, is continuation of natural law, based on the priory knowledge. At last, the state court was of interest of the most people. Domination of the rein court promised to people calm life and protected people from wars between seniors and tyranny of feudal lord. Seniors could also address to the rein court to solve some problems. In this case the rein court played the role of independent judge, who followed to the objectives, valid arguments and commons norms.

We suppose that the court of a church represented the culture and the court of a rein

represented civilization. But its very important to take into account, that Christianity concluded idea of linearity of time and, therefore, progress. The European Christianity civilization assumed this idea and kept the connection with culture. So, the law in the European countries admitted as fundamental norms of Christianity traditions. Thus a great number of functions of a state justice have been taken from the church. So, the church had solved the problem of inheritance for a long time, but afterwards the juridical law begun resolving these questions. The family law is based on the wedding. Religion idea of swear underlies to the contract law. The church authority under sins is the basis for the criminal law. This connection between the court of a church, the court of state determined the connection between culture and civilization.

So, the country and the legislation, as major principle of state life, has provided development of science and its rootage in the social entity.

At the same time the science, as the essential part of civilization, based on civilization, couldn't obtain the position of independent exploratory sphere, which follows its proper immanent principals. More than that, the science has become the means of strengthening norms of civilization and in many cases getting rid of the very cultural principles, values, which are realized in the process of spiritual experience development. On the one hand, this way leads to simplification of social relationship, reduction of price of manufacture. However on the another hand, in this conditions a human obey the common standards, norms, which are not always constructive.

The science having become the servant of civilization started to provide it with innovations, which the civilization can't exist without. Indeed, the civilization having turned to the science, as a condition for survive, became dependent on the science.

The civilization itself is one of the forms of social organization, but it doesn't explore the world and doesn't discover its

laws. However the civilization uses the discoveries due to the science, which find privileging conditions for development. So, the civilization makes favorable condition for the science, which provide the civilization by scientific innovations and leads to civilization existence. While the civilization tends to scientific researches it can develop successfully.

In the course of coalescence of the science and the civilization the first presented to exploitation of the physical world, following requests of the civilization starts its great exploitation. No wonder, that the idea of human's domination in the nature has become the trait of the industrial society [5, c. 176]. As a result the scientific progress, permanent growth of demands of civilization industrial society is last stage for realization historical project – transformation and organization nature as the material for supremacy [6, c. 262].

The striving of the civilization for domination under nature leads to the situation when nature becomes inimical for a human. Being used by science it turns to the destructive power which suppresses human mind. But civilization turned this situation to its own advantage, and suggested the society should perceive the science as a give for technical and ecological solutions. The developed industrial society is growing and progressing just because it supports danger [6, c. 255]. At last the system of civilization itself and the character of the science itself lead to such an idea of the state: the development of the mental and material needs, which have obtained ancient ways of struggle for existence are considered to be the most effective method of war for liberation. Civilized society values, put into human mind, assist human development in a certain direction, but at the same time they form a psychological dependence on the science, incapability to imagine state life without science. As a result the science has found a nice place for its development in the conditions of civilization, and in such a way has turned out into so called "parasite" which the state can't live without. Nevertheless the science

depends on the civilization as well as the material resources for the science development are provided only by the state needs and strength.

Civilization defines the rhythm of human life. So, the philosopher Augustine Avreliy (353-430) who lived in the antique world from the historical point of view, wrote, that there was no past – its had been over, there was no future – it hadn't started yet, there was only present. However the present was so fast, that people could not realize it. Indeed, rhythm of time in the civilization is very quick. The progress of life suppresses the person's identity, which as a rule is unable to reflect numerous laws, material combinations which have been discovered by the science, in its mind. The information wave of the science overwhelms the person in such a way that the letter is incapable to understand it fully. So, in the modern world the mankind receives 45 000 pages of new instructions, it takes so much time to analyze all the pages that there is no time left for reflective reasoning.

Nevertheless the science obeys civilization. The subordination of the science by civilization expresses economical dependence on the state. Besides, other forms of the society cannot have necessity in the innovations and scientific knowledge. That is why the civilization crisis is not reasonable for the science. However there is no place for a human in the correlation between the science and the civilization. That is why one needs to find the ways of cultural and humanistic rootage in civilization. These values are main basis of the human existence. Development of any system must have stable fundament independent from the physical world. In this contest we agree with F.M. Dostoevsky point of view: none of the people can be organized on the principles of the science and reason. [7, p. 243].

So, today the main task of scientific humanistic knowledge is the search of unchangeable cultural basis for civilization development. The difficulty lies in the feature of human's nature, which is very different

from the nature of the physical world. The science, turning the main concerns of people on the physical world, has made a human dependant on the material world. People look for their place in the outer world, but fail to find it, because there is no such a place. A man addresses to the science for solution of this difficulty and has become the essential part of this world. However there are death and safe in the world, which rules are explained by laws of the logic and science. However these cases of death cannot be understood and perceived as a normal thing by men, who have the idea of immortality and perfection. The human can imagine more, than nature has in reality. The individual and the nature obey different rules. The laws important for the nature can't be of effective use for an individual, and vice versa, the laws significant for a man can be unproductive for the nature. Course, the death and suffering have explanation in the science, for example, medicine disciplines, but the doctors cannot solve the problems of death and suffering, because the reason of these problems lies far from the science. There is no use to find a remedy for AIDS, when in South of Africa one can observe women violence every 90 seconds or lets take Sudan, where Moslem soldiers got money from their government for the violence under Christian women in time of The Civil war. [8, p. 20]. The attempts of the sociologists to organize the democratic living in the African countries seem strange, because for the most of population the war is considered to be the way of life and way of thinking. To resolve modern problems one should work out the conception of scientific knowledge usage in accordance with spiritual demands of an individual. At last we need the analysis of scientific ideas on the level of political government of the state. Only in such a way science will become sensible and will be a real power of life development.

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ON INTERCONNECTION OF SOCIAL CAPITAL, ORGANIZATION CULTURE AND LEVEL OF ECONOMIC DEVELOPMENT OF NATIONAL ECONOMY

Osik Yu.I., Aimagambetov Ye.B.

*Karaganda Economical University of Kazpotreboyz
Karaganda, Kazakhstan*

The matter of economy development level and informal institutions – components of organization culture - interconnection has been investigated. With this purpose the relations between social capital and organization culture based on their common traits: the multilevelness, distribution through social networks, function of information distribution and information asymmetry elimination, have been considered. The possibility of the organization culture estimation through quantitative characteristics of social capital has been substantiated.

In present-day economical science the so-called “non-economic” development factors attract more and more research workers. Among them the first place is taken by social variables bringing more and more evidences for the fact that a profitable development of the economy doesn't seem to be possible without consideration and cooperation with not only political, but first of all social institutions. The expectations, that for providing a sound socio-economic development a set of ambitious scientifically grounded and successfully realized government programs is enough, are left in the past. Certainly, we can't do without them, especially in the first stages. But the formation of healthy and dynamically developing civil society for achieving this aim is not less important. The role of the state at that retains, but is modified and is in creation of favourable conditions for the formation of the mentioned society.

The functioning in real conditions civil society always rests on human traditions, customs and ethical standards which are the manifestations of culture in national, ethnic, religious and other levels, inclusive of the world's one. Administrative and political measures are able to influence the civil society only indirectly and most often require careful nurturance with special care and respect to national and other cultural peculiarities [1, p.16].

It does not admit a doubt that the importance of cultural differences in the age of globalization will only grow as the world is moving towards a collision, to a competition

of not ideologies, not economies, but cultures, which are becoming the elements of both primary human self-definition (according to S. Huntington [2]) and protectionism. By virtue of the abovementioned a new subject of the research in the economic theory becomes the organization culture as a certain cultural construct.

In works of Kazakhstanian and foreign researchers there are no methods of measuring the organization culture economic parameters. One of the main reasons for it is the fact that the organization culture influences the economy not directly, but indirectly. It seems to us, that solving this problem is possible if considering the organization culture in the context of institutionalism. For the majority of foreign research workers the identification of institutions and organization culture doesn't seem to be possible. One can suppose, that this discrepancy is partly caused by the term's “institution” comprehension duality – as game rules in the society and as the organization (structure) providing these rules' implementation. If we take the institution for the structure, and the institutes – for the “game rules”, this contradiction can be solved. Then the organization culture – some rules of conduct and actions can be presented as the system of different nature and hierarchy level institutes. But for the studied by the institutional economics institutes there are correspondent (objective) institutions, and for the organization culture there are no such ones. How are the “game rules” distributed within the organization culture if not through institutions? There are two prin-

cial directions of information distribution: horizontally and vertically. Vertically the information is distributed in hierarchy structures, the majority of formal organizations representing them. In the informal entities the information is distributed preemptively horizontally – through social network. It brings together the organization culture and social capital. But, when meaning an aggregate of institutes representing certain “game rules” by the organization culture, the social capital is seen as a resource found through using these rules via the aggregate of the social networks, which are used by individuals for private and collective profit. The social network concept is the most natural for the description and building a social structure.

There are various definitions of the “social networks” notion. Networks are stable structures of direct interaction between people; institutes are the rules by means of which such interactions are carried out (a set of interdependent norms), and confidence – is the expectation that the other will act in our interests [3]. In the extensive treatment of this term the “social network” is defined as a plurality of points (or members of a social system) and the aggregate of the relations depicting the communicative transactions between these points. The social network can be considered as an integral one, where the complete structures of the role relations in a social system are described, i.e. the networks of the whole community restricted by formal and informal frames are regarded simultaneously. The social network can be considered as a personal one, where an individual, other individuals, who he is having relationship with, and communicative transactions between these individuals, i.e. only personal relations of an individual are regarded and the studied network is limited by the informal frames of a concrete individual’s personal relations. A personality’s or a group’s behaviour is explained as a derivative of the social networks, the elements of which it appears. In both prospects the investigation of social networks is of practical importance, as, finally, one can define their

role: the influence on the process of socialization, self-identification and mechanisms of social activity. It contributes to a deeper understanding of not only the interactive activity of individuals, but also the social structure as a whole.

The network analysis school developed on the basis of A.R. Radcliffe-Brown’s works in western science. Further on, the notion of social network was actively used by E. Bott, F. Meyer, B. Poe, A. Meyer, M. Shrivani, A. Betey-Barness and a group of investigators known as the Michigan School of Socio-Network Analysis [4].

As F. Fukuyama believes, the networks’ features are in the fact that their participants share special norms and mutual help values, whereas the hierarchically built organizations are founded on the deprived of these norms formal authoritative vertically built relations [1]. The similar norms and values lay in the organization culture [5].

For the socially structured processes study M. Granovetter has worked out the social networks analysis method, hypothesizing about the “weak relations” great importance (strength of “weak relations”) for the information and influence distribution compared to “strong relations” – (kindred, friendly ones) [6]. In “thick” networks, “weak relations”- mediated, the information concerning an individual’s behaviour is distributed more quickly and effectively. At that, there are more possibilities for the behaviour shaping left, inclusive of those owing to generation of standard, symbolic or cultural structures, which influence the behaviour. One of the principal ideas of M. Granovetter lies in the fact that “weak relations” are vital for the integration into the modern society. Thus, “weak relations” are the organization culture bearers in the broad sense of the word, i.e. not only at the level of organization, but also in the meso- and macrolevel.

It should be emphasized that social networks are not only the source of information, means of its asymmetry remedy, but also the source of confidence and the channel, through which the realization of economical,

cultural, social and symbolic capital and their conversion are effected. It is possible to say that “weak relations” form the one informative confidential field. But with no “weak relations” the social structure elements are dissociated, quantified, and the one informative confidential field in such a social structure lacks even with a great number of “strong relations”.

Up to the present day the organization culture in the economic science, particularly in management, was considered at the micro-economic level – at the level of a firm. In this narrow-minded, original sense of the word it had been interpreted. It was meant, that the investigation of another main economic agent – housekeeping (family) – is a sociology object. The informal relations appearing at the macrolevel, for example, at the national level, out of formal organizations, were also referred to sociology.

We confirm the following: by means of the organization culture the kindred and friendly social relations (“strong relations”) form economic contacts in elementary units of social environment – in families, among friends, relatives, i.e. at the microlevel. By means of the organization culture the “weak relations” form economic contacts at the macrolevel. At the first approximation this is the national level, but taking into account that the organization culture formation is founded on the positive ethics, wherein we offered the meso- and macrolevel distinction [7], one can mark some sublevels of the organization culture realized by “weak relations” – ethnic, religious, branch, etc.

The organization culture is realized through social capital and determines the resource residing in the relations (networks), which we support. Not incidentally its operationalization takes course via the “social network” category. Which is to say, it is equal to the sum of relations of an individual with other individuals and is a mediator for other resources’ mobilization. This is social networks, where the conversion of the social capital occurs (its transformation into other nonmaterial and material forms), and also its

measuring, which is made by means of the degree of involvement into some or other networks of relations and characteristics of these networks themselves.

The consideration of different countries’ organization culture social networks’ influence on the development of these countries’ economies allows interpreting some significant characteristics of the organization culture differently, “individualism – collectivism”, in particular. According to G. Hofstede’s [8] research the Japanese organization culture is characterized by the high level of collectivism; moderate individualism, which is expressed most strongly in the USA, is peculiar to the employees of Western Europe countries. Taking into account the indisputable fact of the collective labour privilege over the individual one, the results of the above-mentioned author’s research don’t shed fresh light on how such an “individualistic” country as the USA have reached the highest level of its economic development and goes on keeping it for a protracted period of time. We maintain that the consideration of organization culture through social networks, wherein its main resource – confidence – is being converted through the immaterial form of the capital – social capital – into its other material forms, is of great importance as it casts light upon the nature of individualism-collectivism. It is also worth paying attention to the conformity criterion used in sociology and not used in the economic science so far.

In the being below quoted politico-economical investigation “Confidence: social virtues and avenue to prosperity” [1, p. 108] on the ground of apprehension the essence of social transformations in the societies of some countries interrelated with economic growth F. Fukuyama brings out clearly that the family accommodates the economic growth not always. He not only appeals to the minds of social scientists of the past, who included the strong family in the number of the economic growth deterrents, but also confirms it by means of historic-economic research of some countries’ development. “... in China or some regions of Italy the family

means much more than other culturally enrooted forms of human association, and the specified circumstance influences greatly on the economic life of these societies. As recently started accelerated development of the economy of Italy and countries of Chinese culture has shown, if the rest cultural values are in good and due form, the very domesticity is neither the barrier for industrialization nor for the rapid growth. However, domestic-

ity does influence the character of this growth, and namely on the available forms of production organization and what branches of the world's economy the country can occupy its niche in. Family oriented societies undergo serious hardships while creating large economic institutions, and it, in its turn, restricts the possibility of field choice in the global market." The above said can be illustrated by Table 1.

Table 1. Interconnection between the ways of socialization manifestation, business function type and level of economic development

Socialization way	Organization business activity type	Economic growth favour	Large enterprises' creation favour	Long-term development favour
Through family and kindred (informal networks with "strong relations")	Family business	In initial stages of development	-	-
Through voluntary associations of unrelated type (informal networks with "weak relations")	Corporate enterprise with professional managerial system	In all stages of development in long-term period	+	+
Through government (formal networks)	Governmental or financed by government enterprise	In short-term period	+	-

Note: composed by the authors on the ground of: Fukuyama F. Confidence: social virtues and avenue to prosperity. – Publishing House AST "Yermak", 2004 – p. 107.

Both in the West (from M. Weber to C. Clark) and in the East it was popularly believed that the role of a strong family in the development of "high" economy was categorically negative and weakening of family unity was a precondition of the economical progress. Soviet, Chinese and other communists hoped to weaken strong positions of the family by means of stimulation and inculcating other forms of devotion – to the commune, party, state. However, the idea of the only path of socio-economic development of the society under modern conditions of economic activity globalization – through nuclearization and family decay – doesn't find prevalence. For the substantiation of this opinion F. Fukuyama makes reference to the Historian of Economics Gershenson A. who noted that the model of comparatively late modernization of Japan and Germany essentially differs from the earlier one put into the

effect in England and the USA: "in stimulating the development of the first two mentioned countries the most active role was played by the government [1]. Other Historians testified that the "nuclear" family had been far more widely popular in pre-industrial societies, than it had been thought earlier. Somewhere the kindred groups fell to pieces, first, but then, with the industrialization, they were restored again [9]".

The consideration of organization culture through a system of networks allows finding cases for the thesis that not the criteria of the absolute level of family development (from highly structured, 3- and 4-generation family – to the nuclear one) determine the potentiality of socio-economic development of the Nation, but its position in the hierarchic system "family – intermediate formal and informal institutions – state". If the priority of the family provides the initial

push towards economic development, the priority of the state and formal economic institutions provides the economic development in the short-term period and up to a defined limit, then the priority of the civil society provides the highest result – the sustainable development in the long-run period, but upon the condition of the proper sophistication of the two previous forms of socialization.

Let us consider the organization culture conversion into the material form – economical goods.

F. Fukuyama gradually and demonstratively lets us down to the fact that the hegemony of the family (and, in a certain sense, generation) over the other social institutions puts a range of restrictions on the economic development of such culturally having so little in common countries as China and Italy.

The Chinese enterprises are small-sized, are usually in the ownership of a family and are managed by it as well. A strong familism of the Chinese society, the principle of equal inheritance distribution between the sons, lack of adoption mechanism and distrust to strangers – the combination of these factors has led to the formation in traditional China of a certain economic activity system, which in many instances anticipated the business relations culture in contemporary Taiwan and Hong-Kong. There were no big estates in the rural area – only microscopic allotments keeping on dividing in the following generations. The families were constantly going through periods of rise and fall. The hardworking, economical and talented made fortune and moved upwards the social ladder. However, in the next generation the family property could disappear after its being divided between the sons. H. Baker, an anthropologist and explorer of Chinese rural living, noted: “No one family in our village was able to own one and the same amount of land longer, than in three generations.”

The reasons of this phenomenon can be excluded neither from the present-day Chinese societies’ development level nor from the lack of modern and legislative financial

institutions, as other societies could come out the boundaries of the family in their business life organization, even having a far more low level of development and far more weak institutions. Here F. Fukuyama finds the explanation, which is difficult to contradict: the Chinese business modern structure roots in extraordinary position of the family in Chinese culture [1, p. 160].

In some regions of Italy, as in Chinese societies, family connections turn out to be stronger than the other ones not based on social relations types’ kindred, whereas the quantity and the role of associations taking the intermediate position between the state and the individual turn out to be comparatively insignificant, that testifies to a steady distrust to the people, who are not the members of the family. Consequences: the private sector enterprises retain their small sizes and remain under the control of one or another family; large-scale firms need a constant governmental support.

A social life description in a South Italian town of Kiarment is the confirmation of the above said. “The most reasonable attitude to the people who don’t belong to the family – is suspiciousness. Any head of the family knows that other families will envy his family, be afraid of its prosperity and seek for an opportunity to work a mischief to it. Therefore, he should be afraid of them and be ready to make harm to them, diminishing their chances to harm in the future, as well [10]”. There is also a phenomenon observed in other atomistic societies with relatively underdeveloped middle level organizations in South Italy: the most powerful associations are crime families.

D. Lendes maintained that France owes its relative underdevelopment against England, Germany or the USA to the predominance of such a traditional form of job management as family business in it [11, p. 623].

Let us consider forms of labour organization in another couple of countries – seeming to be antipodes from the point of view of culture and socialization – Japan and the USA. In economical patterns of these coun-

tries the predominance of large corporations, government owned or sponsored only occasionally, is in common. They were formed comparatively early: at the beginning of 1830-s – in the USA, in the last decades of the XIX century – in Japan. The direct opposite of Japan and the USA is a myth as F. Fukuyama maintains. And he gives evidences to it. So, A. de Torquille recorded in the 30-s of the XIXth century: “Against the background of the other Western countries the USA show up the existence of the voluntary organizations’ branching network: churches, professional federations, charities, schools, hospitals, universities, saying nothing of the economics with its strong private sector. If it is needed to inspire some ideas or encourage some feelings by virtue of a good exercise, they (Americans) make a society right away. Here and there, where at the lead of a serious undertaking you see the government in France and a made man – in England, you are sure to find a society in America [12]”. At the end of the same century M. Weber announced that “the sign of the very American democracy had been the fact that it had connoted not an accidental gathering of individuals, but a lively active complex of voluntary – though eagerly protecting their autonomy – societies [13]”.

The following coincidence appears to be interesting: though Americans do not give up their habit to unite into voluntary organizations, both traditional forms of voluntary associations and the family have been remaining in stable decline in the last decades. Evidently, there is an interrelation between the first and the second. Here it is pertinent to note that M. Granovetter offered a quantitative characteristics of the social capital at the National level, the main variable of which is the reduced quantity of social organizations [6].

If we get down to facts, then it appears that the role of the government in Japan is a priori corrupted and exaggerated. That is not the case that the government in Japan allows itself tampering with the life of the society more often than in the USA, but the case is

that the society itself, from corporative associations to average citizens, regards the governmental resolutions with a greater respect. And over the period of many years the Japanese index of the public sector contribution to the GDP is the lowest one among the OECD member countries and is lower than in the USA [1, p. 96].

The data testifying to the doubtfulness of the thesis about the steady Japanese uniqueness, insularity from the Western culture are given. The Japanese uniqueness is initially far more flexible and “isomorphic” to the West, than it is thought about. For example, “the essence of samurai spirit in modern corporative association – the attitude to one’s own concrete work as to a creation” [14, p. 85] looks like an analogue of Protestant work ethic. The likeness deepens by the tradition of systematic self-trial: the Protestantism contains a drive to constant trial, but the Japanese perceive the effort, tiresome performance of duties and hardships as character strength test: those who turn out to be the most tolerant and devoted to their own work are considered suitable for forge appointments. As one more of the Japanese development traits one can mark their “adoptibility”, desire to study foreign experience. Already at the beginning of the XXth century “an amazing gift of the Japanese to adapt European Science and establishments to their needs” [15, p. 26] was a matter of common knowledge. The father of a well known “Japanese” system of quality circles was an American W. E. Deming, and the emphasized as a modern Japanese economics feature principle “a firm is a family” has firmed itself up due to the life-time hiring system, which, according to the estimation of the “Sony” Company President Akio Morita, “was actually enforced... by the labour laws established by the occupation authorities, when from the USA to Japan for the purpose of demilitarization and democratization of the country many cost controllers holding to liberal leftism were sent [16, p. 193]”.

In the light of such inconsistencies between the ideas about collectivism – indivi-

dualism, the organization culture dynamism prevailing in the USA and Japan, formed by G. Hofstede on the ground of the developed by him methods and a range of other research workers on the one hand, and the factological material given by F Fukuyama and the fore-quoted other authors on the other hand, the position of the last appears to be more reasoned and deeply investigated one. Besides, it is in agreement with our idea about the organization culture macrolevel, the possibility of introduction of more readily available, comprehensible and unsophisticated criteria of its estimation, especially through the social capital determined using the idea about the structure of social networks and quantitative criteria of its determination. In the social networks' structure the quantified "strong relations" and the continuous field of "weak relations" are distinguished.

Thus, the organization culture and social capital have some traits in common: multilevelness, distribution through social networks. They perform the function of information distribution and information asymmetry elimination. They are closely connected: following the complex of rules (institutes) within the organization culture at the communication by means of social networks leads to the social capital cumulation. The last, as the non-material form of the capital can be transformed into other forms, monetary-material one among them. The organization culture development level estimability through the quantitative characteristics of the social capital follows thence.

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SATE AND TRENDS OF THE GAS SECTOR IN THE WORLD FUEL-ENERGY COMPLEX

Surzikova O.A., Nikulina I.E.

Tomsk polytechnical university, Tomsk, Russia

The paper present statistical material and analysis of one of the natural fossil power resources – gas. A situation of gas stocks in various regions and countries, dynamics of its extraction, consumption, export, import and average annual prices have been analyzed for the past several years. In addition trends of the world gas sector for the nearest future have been considered.

The International Gas Union values the world natural gas reserves at about 400 trillion cubic meters, while confirmed reserves make up only about 170 trillion cubic meters [1]. The world explored reserves in [2,3] (table 1) make up about the same value.

The largest reserves of gas are in Russia (27,4%), Iran (15,4%), Qatar (14,9%), Saudi Arabia (3,9%), the United Arab Emirates (3,5%), the USA (3,3%), Nigeria (2,9%), Algeria (2,8%), Venezuela (2,5%).

Dynamics of increase in the world reserves of natural gas is favourable. Thus, confirmed reserves in 1983 were 92,68 trillion cubic meters, in 2003 – 175,78 trillion cubic meters [4]

State-of-the-art technology of natural gas production (table 2) guarantees explored reserves of gas to the world community for 63 years [5].

Table 1. World explored reserves of gas, dated of beginning of (milliard cubic meters) [3,4]

Regions	Europe and Russia	Asia	Africa	America	Oceania and Australia	Total
Capacity	54002,1	86944,1	14085,3	14577,3	4066,8	173675,7

Table 2. Dynamics of natural gas production (milliard cubic meters) [2,3]

	1995	1997	1999	2000	2001	2002	2003	2004
Total	2624,2	2696,4	2851,9	3079,5	3156,0	3202,7	3313,1	3414,2

As you can see fro table 2, natural gas production has increase by 30.1% from 1995 to 2004.

The following countries have got the largest capacity of gas production: the USA (20%), Russia (19,2%), Canada (6,3%), Al-

geria (5,3%), Iran (3,9%), Norway (3,7%) Great Britain (3%).

Gas use in the world is constantly rising. According to [2,3] its consumption has increased by 30% from 1995 to 2004 (table 3).

Table 3. Dynamics of natural gas consumption (milliard cubic meters) [2,3]

	1995	1997	1999	2000	2001	2002	2003	2004
Total	2221,6	2343,2	2430,7	2495,6	2531,2	2604,0	2685,2	2779,7

Table 4. Dynamics of export (a) and import (b) of natural gas in the world (milliard cubic meters) [2,3]

		1995	1997	1999	2000	2001	2002	2003	2004
Total	a	493,0	520,8	564,1	617,8	609,4	706,6	748,7	789,9
	b	491,9	521,6	563,0	625,4	654,0	706,8	740,9	780,9

The largest gas consumption falls to the share of the USA (22,7%), Russia (15,9%), Great Britain (3,7%), Germany (3,6%), Canada (3,4%), Iran (3,1%), Japan (3,0%), Italy (2,9%).

The largest capacities of gas export falls to the share of Russia (25,1%), Canada (13,3%), Norway (9,6%), Algeria (7,6%), the Netherlands (6,8%), Turkmenistan (5,3%), Indonesia (5,0%), the USA (4,9%).

The biggest importers of natural gas are the USA (15%), Germany (11,4%), Japan

(9,7%), Ukraine (8,8%), Italy (8,5%), France (5,7%), South Korea (3,8%), Spain (3,4%).

In the nearest thirty years the following countries are likely to have the most rapid rates of gas consumption growth: China (5,4% per year), African countries (5,1%), countries of South Asia (3,8%), Latin America (4,1%). Demand in the countries of the Organization of economic cooperation and development (OECD) will grow more slowly: Western Europe–2,1%, Asian-Pacific region (APR)- 2,3%, USA and Canada – 1,7%.

Table 5. Forecast of the world demand for natural gas [6]

	2002	2010	2020	2030	Average annual rates of the demand growth, %
	Milliard cubic meters				
World, total	2622	3225	4104	4900	2,3
OECD	1380	1624	1924	2154	1,6
North America	759	866	1002	1100	1,3
Europe	491	585	705	807	1,8
EU	471	567	684	786	1,8
APR	130	173	216	246	2,3
Countries with transition economy	635	728	863	984	1,6
Russia	415	473	552	624	1,5
Other	220	254	311	360	1,8
Developing countries	597	864	1307	1753	3,9
China	36	59	107	157	5,4
Indonesia	36	53	75	93	3,5
India	28	45	78	110	5,0
Other Asian countries	109	166	242	313	3,8
Brazil	13	20	38	64	5,8
Other countries of Latin America	89	130	191	272	4,1
Africa	69	102	171	276	5,1
The Near and Middle East	219	290	405	470	2,8

Because of a rapid rate of gas consumption in developing countries, first of all, in China a geographic structure of gas consumption will change. A specific gravity of OECD countries in the world consumption within 2000-2030 will reduce from 52% to 49%, for countries with developing economy – from 24% to 19%, while the share of de-

veloping countries will rise from 21% to 32%.

A branch structure of gas consumption will change. Within 2000-2020 the demand for natural gas in the world electrical power engineering is likely to rise rapidly, with an annual rate of 3,2%. This will involve increase in a specific gravity of natural gas in

fuel consumption in electrical power engineering up to 27% as compared to 21% in 2002 (in 2030 - 29%). Transition of the world electrical power engineering to gas will ensure rise if the coefficient of efficiency of a plant up to 62% (2030) in comparison with the coefficient of efficiency of a plant, running on coal (43-44%). This process will be especially fast in European countries where a specific gravity of gas in energy resources consumption will increase from 15% in 2000 to 41% in 2030.

Gas consumption in an industrial sector will distinctly rise, especially in petrochemical industry where gas is used as a raw material. By 2010 an expected minimum volume of gas processed to liquid synthetic fuels is going to make up 29 milliard cubic meters as compared to 4 milliard cubic meters in 2000. By 2030 gas consumption for these purposes will make 233 milliard cubic meters.

An increasing demand for gas responds to the interests of OPEC, The Organization of the Petroleum Exporting Countries, where the world largest gas stocks are accumulated (42% of the total stock), while they are producing just 14% of the worldwide gas production.

Introduction of condensed gas fuel (CGF) in the international trade is going to develop rapidly. At present the CGF share in the international trade of gas is 27,4%. By 2020 the CGF share in the total capacity of gas market is expected to rise up to 31-37%. Export of CGF to Asian countries is about 70% from the total capacity of CGF in the international trade channels, about 27% of CGF are exported the Western Europe countries, the rest - to the USA. At the moment the growth rates of CGF demand is almost twice as high as a demand for pipe-line supply. In 2002 gas import via pipe-line systems increased by 2,6%, while the CGF supply - by 4,3%.

Increase in the growth rate of CGF trade is caused by a significant reduction of prices on this type of fuel. For the past ten years a cost price of production and transpor-

tation of CGF have been reduced by 35-50% and a reduction trend of expenses still remains.

The first stage of CGF trade development was stipulated by impossibility to produce fuel by another method. At present there are a number of other reasons: assurance of supply instead of depleted own resources and a wish diversification of importing resources.

Markets of natural gas are regional since gas supply is tied to pipe-line. However, rapid spreading of CGF trade is likely to globalize this market. At present CGF prices are fixed for each transaction. Though, it is not inconceivable that prices on condensed gas will be exchange quoted.

An American consulting company «Cambridge Energy Research Associates» («CERA») is expected that in medium-term outlook CGF production may become the second important business in the global electrical power engineering sector. This is caused by two factors – sharp rise in supply and increasing demand worldwide, especially in the USA. By «CERA» calculations in the nearest 8 years it is necessary to build up production capacity of CGF the same as was built up from the past 40 years. At the moment production capacity of CGF in the amount of 60 million tons per year have been already coordinated and are at the construction stage in Asia, the Near and Middle East and in countries of the Atlantic region.

Expansion of production of CGF is caused by intention of the countries with significant stocks of natural gas to actively use with a view of profit maximization. Qatar, Nigeria, Trinidad and Tobago, Australia are among these countries. Development of production is also possible in Iran, Angola and Venezuela.

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Materials of conference

INFLUENCE OF FISHER'S EFFECT ON BANK STRATEGY

Arzyakov V.I., Arzyakova O.N
The Ural state technical university,
Ekaterinburg, Russia

The analysis of management of the percent rate of and account in it of inflationary risk - one of major tasks of forecasting of bank activity in changeable conditions of market economy. Thus during inflation there are processes of implicit redistribution of the incomes between the creditors and borrowers (Fisher's effect) according to a known principle of game of two persons to the zero sum.

For an example the situation arising in some conditional typical bank is considered: for simplicity of the analysis was considered, that the bank works with means of the physical persons and finances of the extremely legal persons; real specific profit in a chain " the investor - bank - the borrower " in conditions of a varied rate of inflation requires reassessment of cost of actives for each of the creditors; on an example of the conditional contributions and credits of volume in one rouble we shall analyze process of their depreciation as a result of inflation.

The performance of the given analysis is broken on three stages.

At the first stage the part " the investor - bank " Below, in tab. 1 is examined, the accounts of the incomes of the investor and bank under the conditional

rouble contribution for the period 1996-2007 are given., where are used given Central Bank of Russian Federation under the interest rates in appropriate of year. Examined conditional typical bank (as the borrower) offered the investor (as to the creditor) some profit under the contributions. And the bank nominated the underestimated rates (except for 1996). The investor, agreeing on the offered conditions, lost the real incomes, which were distributed for the benefit of bank. Thus, the percent-price strategy of bank in a part rouble deposit in the researched period did not take into account interests of the investor expecting for protection of the contribution from inflation, and was not balanced up to 2000. After 2000 the percent-price strategy has relative equation, though the investors and carry the losses, but they are not so significant, and the appropriate interest rates specify that the contribution of money resources to bank is more favorable form of the savings of means of the physical persons. Since 2001 and about today the bank receives the rather low latent income, which is caused small deposit by the rate. It, in turn, specifies relative equation of percent-price strategy, and also on steady development of bank sector.

By development of percent-price strategy the special meaning is got by the bottom border of size of the percent rate compensating the level of inflation, which is defined recognizing that the final income of investments should be equal to zero.

Table 1. Dynamics of the investor incomes and bank under the conditional rouble contribution

№	Index	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007 prognosis
1	Deposit rate of percent, %	26,35	11,3	24,57	20,47	11,15	11,15	11	9,8	9,2	8,4	7,7	7,5
2	Contribution, rouble	1	1	1	1	1	1	1	1	1	1	1	1
3	Contribution with the income, rouble [3]=[2](1+[1]/100)	1,26	1,113	1,246	1,2	1,11	1,11	1,11	1,1	1,09	1,08	1,08	1,07
4	Rate of inflation, %	16,41	11,53	84,14	36,59	20,25	12,1	10,2	12	11,7	10,9	8,8	8
5	Real contribution with the income, rouble [5]=[3](1-[4]/100)	1,06	0,98	0,2	0,76	0,89	0,98	0,99	0,97	0,96	0,96	0,98	0,98
6	Final income of the investor, rouble [6]=[5]-[2]	0,06	-0,02	-0,8	-0,24	-0,11	-0,02	-0,01	-0,03	-0,04	-0,04	-0,02	-0,02
7	Final income of the investor, % [7]=([6]/[2]) 100	6	-2	-80	-24	-11	-2	-1	-3	-4	-4	-2	-2
8	Latent income of bank, %	-6	2	80	24	11	2	1	3	4	4	2	2

The formula for it account (in shares of unit) is those: $r_i = \frac{Inf}{1 - Inf}$, where r_i - compensating rate of inflation; Inf - rate of inflation (in shares of unit) in the examined period.

According to a technique of an estimation of Fisher's effect, the real final income D can be determined from a relation $D = v(1 + r_n)(1 - Inf) - v$, where D - real final income; v - size of the contribution; r_n - the deposit rate of percent. With the account, $v = 1, r_n = r_i, D = 0$ is received the dependence

$(1 + r_i)(1 - Inf) - 1 = 0$, i.e. compensating rate of inflation $KIIC = r_i = \frac{Inf}{1 - Inf}$. The meanings, designed on given dependence are submitted to tab. 2.

From the given results follows, that the interest rate under the rouble contributions in 2000 compensating a rate of inflation, should be above actual (make 25,39 % instead of 11,15 %) in case of equilibrium strategy. Thus, with the purposes of a covering of the losses because of a high level of inflation at a rate of 20,25 % by bank should be nominated the interest rate above than level 25,39 %.

Table 2. Settlement meanings of the rouble interest rate compensating an inflation rate

Year	nominal percent rate	rate of inflation, %	compensating rate of inflation, %	deviation of the current rates %
1996	26,35	16,41	19,63	6,72
1997	11,3	11,53	13,03	-1,73
1998	24,57	84,14	530,52	-505,95
1999	20,47	36,59	57,7	-37,23
2000	11,15	20,25	25,39	-14,24
2001	11,15	12,1	13,76	-2,61
2002	11	10,2	11,35	-0,35
2003	9,8	12	13,64	-3,84
2004	9,2	11,7	13,25	-4,05
2005	8,4	10,9	12,23	-3,84
2006	7,7	8,8	9,65	-1,95
2007	7,5	8	8,69	-1,19
prognosis	7,5	6,5	6,95	0,55

One of the reasons of the lowered rates can be a post crisis situation of the Russian financial market, which was caused by crisis of August 1998. The bank adheres to percent-price strategy supposing some underestimation of the factor of inflation, that allows it to receive the latent additional incomes in conditions, when the investors are focused in the greater degree on reliability of bank, rather than on reception of the high income on the enclosed means. Such bank strategy was characteristic for banks which are carrying out the activity during 1998-2002.

The deviation of the current rates from compensating rate of inflation became less during 2001-2007, but still keeps negative dynamics. It is connected that in conditions of market economy the bank can not completely undertake the obligations to the investors on preservation of their contributions, because too great the meanings of compensating rate of inflation can which directly depend on rates of inflation.

On the second investigation phase the part of a chain " bank - borrower " for the rouble credit, results of account for which is considered during 1996-2007 are submitted in tab. 3.

The results of accounts for the conditional rouble credit in the examined period testify to the following. In 1996-1997 the credit rates of percent allowed banks to receive the real income of crediting in national currency. During 1998-2000 a high level of inflation, caused by an economic crisis in the country, destroyed the income of banks under the credits in real sector of economy, thus bringing the latent damage to banks. But in these of year the latent advantages were received by the borrowers (in particular, enterprises of real sector of economy taken credits). During 2001-2002 the period of stabilization was observed, when the bank received the real income of crediting in national currency.

On the third investigation phase overlapping results of the first and second analysis stages is carried out with the purpose of revealing parameters of work of bank in view of the real incomes of its clients (depositors and investors - borrowers). Accounts final annual "deposit-credit" for examined conditional bank is submitted to efficiency of through rouble operation in tab. 4.

Table 3. Dynamics of the bank incomes under the conditional rouble credit

№	Index	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007 prog- nosis
1	Credit rate of percent, %	49,08	28	52,35	38,45	20,8	20,8	17	13,3	11,6	10,6	10,4	9,9
2	Credit, rouble.	1	1	1	1	1	1	1	1	1	1	1	1
3	Credit with percent, rouble [3]=[2](1+[1]/100)	1,49	1,28	1,52	1,38	1,21	1,21	1,17	1,13	1,12	1,11	1,1	1,1
4	Rate of inflation, %	16,41	11,53	84,14	36,59	20,25	12,1	10,2	12	11,7	10,9	8,8	8
5	Real credit with percent, rouble [5]=[3](1-[4]/100)	1,25	1,13	0,24	0,88	0,96	1,06	1,05	0,99	0,98	0,98	1	1,01
6	Final income of the credit, rouble [6]=[5]-[2]	0,25	0,13	-0,76	-0,12	-0,04	0,06	0,05	-0,01	-0,02	-0,02	0	0,01
7	Final income of the credit, % [7]=[6]/[2]100	25	13	-76	-12	-4	6	5	-1	-2	-2	0	1

Table 4. Final annual efficiency of through rouble operation "deposit-credit"

Index	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007 prog- nosis
Rate of inflation, %	16,41	11,53	84,14	36,59	20,25	12,1	10,2	12	11,7	10,9	8,8	8
Latent income from deposit operations, %	-6	2	80	24	11	2	1	3	4	4	2	2
Income of credit operations, %	25	13	-76	-12	-4	6	5	-1	-2	-2	0	1
Final income, %	19	15	4	12	7	8	6	2	2	2	2	3

The received parities testify to unprofitableness for examined bank during 1998-2000 the crediting in rouble of real sector of economy at the usual level rouble deposit and credit rates of percent, and also inflation, available a high level, and essential risks of the credits unreturn. However, probably, the given percent-price strategy of bank is connected that the bank in the examined crisis period felt absence of economic stimulus for rouble investments, in particular in real sector of economy, and tried to avoid crediting of the industrial enterprises. An examined example of typical conditional bank during 1996-2007 reflects a general situation of bank sector of economy and confirms necessity of realization " Strategy of development of Russian Federation bank sector for the period till 2008 "¹.

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¹ The application of Government of Russian Federation and Central bank of Russian Federation about Strategy of development of bank sector of Russian Federation for the period till 2008 from April 5, 2005. M., 2005.

ECONOMIC RESULTS OF SOCIAL ASSISTANCE MEASURES PROVISION SYSTEM REFORMING WHEN PAYING FOR HOUSING AND PUBLIC UTILITIES IN TATARSTAN

Butayeva N.V.

Ministry of labour, employment and social protection of the Republic of Tatarstan

Currently, ones of the most acute problems, maybe, for all subjects of the Russian Federation remain the problems of housing maintenance and utilities and social security provision.

For the Republic of Tatarstan in both areas the year 2005 became a turning one, when concurrently with the reform of benefits, one of the factor of which the decentralization of authority for both legal and financial provision of social protection of people from the federal authority level to regions has become, resulted in a substantial increase of the fiscal load on the last and, as a consequence, the necessity of the budgetary resources mobilization, to implement a passage to the 100% payment by the population of economically sound cost of housing and public utilities' services.

The main re forming components have become:

1. Stopping the allocating investment support of the expenditures of the Republic population at large when paying for housing and public utilities' services using the compensation of the difference between

economically sound service cost and real payment by the citizens to the organizations of housing and public utilities' complex.

2. The transference of benefits to the coverage of housing and public utilities services offered in the form of discount, to real money grants.

The result of leaving governmental grants, on the one hand, has become the stabilization of the financial state of housing and public utilities suppliers, payment discipline enforcement with regard to counterparts, promotion of responsibility for the quality of furnished services and realization of economic mechanisms of organizations' management in market environment in full force and effect.

On the other hand, - on the average in the Republic the tariffs' growth for the population in 2005 made more than 60%, in a range of municipalities sizes of monthly payments grew several times. For the purpose of the population life quality heavy drop a decision of additional subsidization of citizens depending on their income was taken by the managerial authority of the Republic.

Currently, additionally to the ill-prosperity subsidy prescribed by the Russian Federation Residential Code two more subsidies are introduced - the subsidy for the restriction of payment growth (maximum permissible housing and public utilities services growth in 2005 compared to 2004 depends on the family income. For example, at per capita income fewer than 2000 rubles per month the payment growth couldn't make more than 20% of 2000, up to 2500 - 30%, etc. Factual charging beyond the maximum permissible one is offset for the citizens from the republican budget) and the aid grant for heating of the over-norm dwelling space (at per capita income fewer than 3200 rubles per month the expenditures connected with the over-norm dwelling space heating are also offset in accordance with the established procedure).

Although the housing allowances program today occupies the main place in the republican system of social protection both in population coverage (the receivers are 9,4% of the families of the Republic) and in expenses - in the budget of the Republic for the year 2007 1,4 billion rubles or 28% of the overall volume of funds channeled by the Republic for the welfare payments financial package have been prescribed for the housing allowances program carrying out, the stopping the allocating investment support of the housing maintenance and utilities enterprises has lead also to cutting down the budget cost on rendering support for the general population while paying for dwelling and public facilities. For 6 months of 2004 the total cost on granting ill-prosperity subsidies and transfer payments for suppliers of housing and public utilities services made 879,2 million rubles, for the same period of 2005 730,0 million rubles (149 million or 17% less) were ordered to pay ill-prosperity subsidies only, including the republican segment, for the

analogous period of 2006 - 538,0 million rubles, 2007 - 460,5 million rubles.

A constant reduction of cost volumes is conditioned by both anticipating, compared to the growth of tariffs on housing and public utilities services, growth of people's incomes (for the period of 1999 real population income of the Republic grew by 55%), and by the toughening of requirement to claimants.

The major part of the population has lost the governmental support when paying for the dwelling, but at the same time the saved assets were redistributed to cover the "republican" aid grants - the enlargement of help to the most disadvantaged group of Tatarstan people.

By the 1st of January 2007 from 258 thousand people- members of the families receiving subsidies 104 thousand (40%) were retirees, 75 193 persons of them - lonely pensioners and more than 59 thousand - non-adults. At that, the carried out analysis testified that 75,3% of the total number of grants recipients were families with the income of fewer than 3 200 rubles per capita monthly (the living minimum wage per capita of the population is 3 023,0 rubles per month). 82,4% of the subsidy bill fell on them, 31% of it making additional "republican" guarantees.

Owing to the use of the compensation factor at the per capita income of a family less than the substandard income, the amount of the maximum permissible part of the citizens' intramural expenditure decreased, in the mean, from 21%, established in the Republic, to 15%. And at the expense of additional republican subsidies, really, it made for the substandard income families not more than 9%. At that, 10% of "the poorest" didn't spend their own funds to pay for housing and public utilities services at all.

When analyzing the situation as a whole, the expenses for dwelling and utilities services in total income of the population of the Republic at large taking into account granting of all kinds of subsidies without benefits in 2004 made 5,9%, under the conditions of payment for services on economically sound cost the given part runs up to 6,7%. In 2005, under the condition of households' total income growth by 133% (on the data of statistical service bodies the average republican amount of the population income made 5 345 rubles per month in 2004, 7 111 rubles - in 2005) the quota of expenditure dropped up to 6,1 %, and inclusive of granting separate families with ill-prosperity subsidies on payment restriction growth and over-norm dwelling space made 5,7%. The specified tendency remained in the subsequent years as well.

An analogous economic effect the "monetization" of benefits on housing and public utilities services payment gave. Until 2005, as it was mentioned above, the benefits prescribed for separate categories of citizens (invalids, veterans of work, families of dependent children) were offered in the form of payment lowering. The order worked, in agreement with which a Social Security beneficiary applied to an asset man-

agement (HUS, HC administration), presented his certificate of the right to benefits and paid the check of housing utilities with account of the corresponding discount factor. The asset managements, in their turn, presented the volumes of shortfalls in income with reference of franchising to the compensation from the corresponding budget.

The services providers were directly interested in compensations volume gaining, that in a range of cases lead, put it mildly, to the corruption of information about the amount of beneficiaries and the size of provided benefits.

From 2005 the order has cardinally changed. The determination of the right to a benefit and its size was given to social protection bodies. As a result, the quantity of citizens having the right to social assistance when paying for housing utilities services decreased by 78 thousand people (10% from the total number of the declared beneficiaries) in 2005 compared to 2004. At HUS payment tariff growth by 60% in 2005 the subsidy-benefit payment cost escalation didn't exceed 9,6%. Real budget savings made about 100 million rubles in 2005.

It should be noted that the population perceived the changes in the franchising system quietly enough. To a large extent it is connected with the fact that the housing utilities services subsidy-benefit volume (in terms of money) has not changed with the new mechanism of benefit granting. The acknowledgement of it one can think to be the preserved in 2005 high level of payment gathering from the population: in February 2005, right after the new social support mechanism introduction, it made 96%.

Probably, it might be incorrect to judge about the efficiency of the carried out reformations without touching the expenditures connected with their preparation and realization.

The main condition to realize the "tatarstanian" experience is an active application of information technologies both in the system of social protection and in the system of HPU.

In the Republic a computer-aided system of address social protection (ASP), the uniqueness of which is in realization of the interaction with many ministries, agencies and service providers, functions. Normatively the same demands for all the participants of the interaction and also the data exchange order have been established. Today the data bank contains the information about the person (first name, father's name, last name, address, marriage status, etc.), the family (composition, family relationship to the applicant), the pensioner (kind of pension, disability, the EDV size in federal beneficiaries), the help rendered to the person (sum, kind of help), the dwelling occupied (housing facilities specific characteristics, kinds and volumes of the provided housing utilities services).

It allows social protection bodies to perform the function and social support payment according to

the principle of "one window" using information technologies. A person addresses a social protection body only, the staff of which performs the reception of addresses, the computation and provision of all kinds of social support. The existing system allows raising the efficiency of administrative costs essentially. The cumulative expenditures on experts' activity provision, inclusive of labor costs, for the year 2007 have been defined in the volume of 92,0 million rubles and it makes 1,3% of the performed by them social support measures – 7,0 billion rubles per year.

The results of the passage to a new system of housing and public utilities services payment by the population and monetization of all kinds of the state social support testify to these works real positive results:

- for the budget of the Republic – in the on-budget expenditures rationalization and the creation of the social support optimal system allowing, without the impairment of citizens' rights at public services cost escalation, keeping down the budget costs;
- for the housing and public utilities branch – in the possibility of strategic development in a competitive environment irrespective of the fiscal capacity;
- for the people – in the state guarantee of timely and full-force-and-effect social assistance provision allowing making payments for housing and public utilities services independently.

The applied in the Republic system of needy people subsidy assistance when paying for housing and public utilities services, is quite effective, in our opinion. The more especially as from 2006, according to the requirements of the Residential Code of the Russian Federation, the Republic has passed to subsidy granting with regional standards use. The payment sizing depending on the regional standard of housing utilities cost (a confirmed value, the calculation of which is carried out using average housing utilities factors for the municipal government, and not real charging of a concrete family) not only simplified the payroll schema, but also became a real motivation for the economical use of public services.

Currently, the preference scheme is less effective, and, first of all, it is connected with the fact that the norms establishing social assistance measures on dwelling and public service payment are contained practically in all laws affecting the interests of separate benefit categories persons. At the same time their formulations differ greatly from each other. Some contain restrictions by the public services consumption rates established by the organs of local authority. There are no such restrictions in the other, for example the Federal law "On social protection of invalids in the Russian Federation". As a result, an invalid, inscribed alone in a large dwelling space cottage, most often being not possessed by him, gets a benefit in the amount of 50% of all housing and public utilities services cost. While a low-income invalid living in a

constraint environment gets a benefit in a considerably less amount. Thereby the social justice principle is violated in the case of citizens reckoned among one and the same category.

Besides, a smooth transfer of a natural benefit into a money grant doesn't inspire the population to public service economy (the less the payment, the less the benefit size).

To our opinion, it would be rational to pass to the calculation of benefits on payment for housing and public utilities services also proceeding from regional standards of normative dwelling area and housing and public utilities cost on the analogy with payroll schema of housing and public utilities subsidies. But the solution of this problem is, first of all, in the sphere of federal authorities' legal control.

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MIXED STRATEGY OF INNOVATION'S DEVELOPMENT OF CORPORATIONS

Makarova S.V., Stepanova N.R.

Ural state technical university, Ekaterinburg, Russia

According to the basic socio economic processes of modern development of a world civilization there was claimed such corporate administrative model, which in an optimum degree would take into account and could realize interests of all social groups, remaining in an equilibrium condition.

The results of activity of corporations are estimated on directions: social, economic, legal and ethical. The social responsibility assumes acceptance of such decisions, which realization raises a standard of well-being of the population and answers interests of a society and corporation. On the integrated standard parameters is capitalization of human resources and increase of quality of life. Such strategy here is inadmissible, when in a favour to momentary benefit the forecasts of rather probable extreme social explosions are ignored.

On other directions of activity of corporations the satisfaction of paymentable demand for the made goods and rendered services to a society, maximum of the profit is supposed at observance of the current legislation without harm to an environment.

For an our times is characteristic the beginning and development of large corporations, in particular of global scale. Such corporations are capable to invite to work of the best experts of all world, guaranteeing them worthy payment of work, quality of life, and also protection of the intellectual property, created by them, and realized in process of innovation activity. Within the framework of such corporations the struc-

tural divisions work as independent economic units, and the central body carries out consultative and coordination functions, renders service of innovation character on removal of the internal conflicts, on creation of a confidential atmosphere.

Certainly, between independent structural divisions of corporation the collision of interests, rivalry is possible. But it not wearisome competitive struggle for a survival, in which compete party essentially weaken itself.

In connection with intensive development for last decades of the theory of the human capital there was a global crisis, during which on change to traditional market values there come social, and on change to financial gamble - real investments in industrial spheres of activity.

The achievement of the theory of human capitalism considerably promote to beginning and development of a civil society in the countries and in separate territories. The modern estimation of maturity of a civil society in any concrete territory and human capital in considered corporation determines model of its management: from initial (absolute submission) up to final (democratic), characteristic for corporations of global scale.

The beginning of the mixed economy in Russia is characterized yet not quite generated, insufficiently proved social and economic interests of labour collective. Therefore corporate administrative structures, basically, work in the interests, not worrying about a transparency of received results in socio economic sphere, not having trust of labour collective and not caring about formation of creative cooperation in corporation.

If earlier business basically was under construction on skill carefully to plan activity and consistently to carry out the developed program, ability in time now is more important to adapt for changes in external environment. There was a understanding of requirement of simultaneous development of a set of the most probable scripts of development. Thus the degree of probability of each script can change rather quickly with the purpose of achievement of an equilibrium condition of corporation.

In modern conditions of innovation development of the mixed economy is claimed and mixed strategy of management. Obviously, in conditions of high uncertainty of socio economic development of this or that territory the variants of the mixed strategy can be rather approximate. But their absence is much worse; it can result to loss of management, to chaos and confusion.

In two-measures (flat) models of management the rate is done on change only of one argument. At the correct forecast of process the greatest possible prize is achieved; at the erroneous forecast - maximal loss.

The mixed strategy is realizing volumetric model, allow to reveal the optimum compromises in a corridor of inconsistent restrictions.

On our sight, the realization of several variants of such strategy is possible.

The first variant: strategy of growth of corporation with criterion of an optimality - reception of the maximal profit and basic restrictions - on paymentable demand of the population, payment by results of work and enclosed capital.

The second variant: capitalization of human resources of corporation and increase of quality of life of families of internal groups of influence (hired workers, managers, proprietors). Criterion of an optimality - maximum of size of the human capital, restriction - share of financial resources directed on development to corporation. The ratings of the basic tendencies of development of a world civilization according to this variant of strategy are annually published by authoritative international organizations in mass media.

The successful decision of the put problems can be promoted by study of experience of work of rather authoritative World trade organization. So, the methods of the analysis of disagreements and mechanisms of the coordination of interests, perfection of the working standards and criteria of an estimation of results of works in view of evolutionary development of the world can appear rather useful.

The third variant: development of innovation technologies in the field of applied scientific researches. Criterion of an optimality - complete satisfaction of paymentable demand of the population in original competitive commodity production and rendered services, restriction –requirement for a highly skilled team, and also possible financial risks.

By development of the mixed strategy of innovation development of corporations the external groups of influence are taken into account: the imperious structures at state and municipal levels, civil society of territories, which are in sphere of influence of corporations. Besides the measures on a case of occurrence of extreme situations (acts of nature, technology accident) are developed.

Thus, the mixed strategy of innovation development of corporations provides presence of its several variants, which realizations is assigned on uniform, though and distributed authority. A possible task of the corporate lawyers is the achievement of trust of all persons interested in successful activity of corporation. In accessible to understanding of all persons the form should be given the convincing and well argued answers to questions: as well as at the expense of that grows capitalization of corporation; what principles of formation and distribution of the profit, social package; what stratification in the incomes of the persons having the attitude to corporation. Besides it is necessary to give the similar information on other corpora-

tions having the same sphere of activity and located in the given region.

What conclusions and recommendations can be made as a result of the analysis of the given information? The attention practice of the analysis and resolution of conflicts arising in the given corporation (what mechanisms of the analysis of disagreements and the coordination of interests) deserves. Rather productive the work on anticipation of events, instead of on traces of the come to pass facts is. In the educational literature there are many such examples.

In result the mixed strategy of innovation development of the given corporation will carry applied character, and the corporate administrative model will have an opportunity of the further perfection and development, in time adapting to quickly varied external environment.

The modern requirements showed to corporations on directions: social, economic, legal and ethical, – are to the full distributed and to its(her) employees. It is necessary in addition to make stress on an opportunity of self-realization, realization of the balanced healthy image of life, preservation of family values.

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QUALITY MANAGEMENT SYSTEM IN THE RUSSIAN INDUSTRIAL COMPANY: DEVELOPING PROBLEMS

Ulyahin T.M.

Tambov State Technical University, Tambov, Russia

Quality Systems are everywhere. In fact, anything that is produced successfully is produced with a quality system (QS). Sometimes the systems are formal (written down), and sometimes they are informal.

A quality system comprises all of the activities that are undertaken to assure that a product or service meets the required standards. The fact is that most Russian industrial organizations is assembling a devices according standard parts and specific brands. These parts are assembled according to an established process. The product is checked, during assembling, to assure quality. Finally, many devices perform a final inspection before releasing it from the industrial organization.

All of these steps are elements of a quality system, and are repeated in all manufacturing and service businesses. The main elements of a quality system are: raw material purchasing and control; incoming inspection of raw materials; process control; final inspection; management responsibility; control of nonconforming product; records.

Formal systems are generally not required in

craftsman endeavors. Craftsman manufacturing involves individuals or very small group who establish their own standards, perform their own work, and verify (or guarantee) the quality.

The actual definition of a quality system from ISO Standards is: "Quality System: The organizational structure, responsibilities, procedures, processes, and resources for implementing quality management" [1].

Feigenbaum [2] provides a better definition: A quality system is the agreed on, company-wide and plant-wide operations work structure, documented in effective, integrated technical and managerial procedures, for guiding the coordinated actions of the people, the machines and the information of the company and plant in the best and most practical ways to assure customer quality satisfaction and economical costs of quality.

The keys to a proper quality system, then, are: company-wide and plant-wide agreement; provides operating work structure; documents an effective integration of technical and managerial procedures; guides the coordinated actions of the people, the machines and the information of the company and plant; assures customer quality satisfaction and economical costs of quality.

Formal quality systems consist of documented procedures to instruct and inform the people involved on how management wants the customers satisfied. These instructions start at the Quality Policy, established by management, and then are implemented through the management system to assure customer satisfaction.

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SOCIAL THEORIES OF MANAGEMENT AND NATIONAL MODELS OF MANAGERS' TRAINING

Shemyatikhina L.Yu.

*Ural State Pedagogical University,
Yekaterinburg, Russia*

Russian conditions of economic development made the problem of professional training of managers actual. What will become the basis of managers' training National model formation? In the present clause the interconnection and interdependence of social management theories and the existing National models of managers' training are considered.

Management and managers are the subject of many sociologists' research. The reasons for such an attention to the topics have become the increase of the role of organization as independently acting subject from the middle of the 50s of the XX century up to the present time. The core of any modern organization is managers integrating separate elements into an effectively working system. As managers don't exist beyond an organization, so organizations cannot exist without professional management.

Social research of management is carried out in three directions: 1) study of managers as elite social group; 2) character of social relations within the framework of managerial hierarchies at enterprises; 3) management as the process of technical and social control in organizations. However, it should be noticed that in the disciplines of Management, Economy, Sociology a range of theories falling out of the field of social research, but representing special interest for a teacher-research worker, as an illustration of possibilities of an interdisciplinary approach to the professional training of managers, develops in the course of time.

Abramov R.N. marked three blocks of such theories offering original views on managers and management. The "Intramanagerial theories" are a part of the managerial science and reflect the evolution of managers' views on their role in organization in different periods of industrial development of the society: scientific management of Taylor F.W., administrative management of Faiol A., cost-benefit principles of Emerson H., human relations school and behaviorism in management, venture management concept of Drucker P., Carnegie school, theory of Bernard Ch. Alongside with the enumerated theories a range of approaches to organizations' administration have been worked out by management: situational, quantitative and process approaches; models of Japanese, American and European managements, results based management, concepts of organization culture, corporative association model, etc. "Futurological theories" considered managers as a social group, which has to take a dominant position in the industrial and postindustrial society: the idea of a technocratic society or technicians' power of T. Veblen (1921), the theory of economic power of A. Berl and G. Means (1932), J. Bernheim's "managers' revolution" idea of the proprietary class's displacement by the class of managers, suppositions of James and Soreff about the priority of an individual's position in the social structure of an organization and the set by this position restrictions on the activity, the model of corporative bureaucracy of A. Toffler, A. Bell's concept of the postindustrial society, where one of the key roles is played by managers. It should be noted that the "technocracy" power ideas of the first and "managers' revolution" ones of the last were especially popular in the period of prepotency of the Keynesian economic model, which provides an active intervention of the

government into the market mechanism and macroeconomic planning introduction, that prepares the soil for the development of governmental bureaucratism and large corporate structures. The Keynesian model crisis in 1970s had led to the decrease of the public interest to the forecasts of the possible leading role of managers in the development of the society.

“Stratification theories” offered different approaches to the research of managers’ position as a part of the industrial society stratification model: the idea of K. Marx about the generation of a new class of “white collars” in industry; the idea of M. Weber about the status group of managers; the theory of Ch. R. Mills about the dominating elite; the research of P. Bourdieu and M. de Saint-Martin on education and top managers’ background, the dependency between basic training of future managers and trajectory of their career.

In all developed nations of the world management is associated with a sustainable and successful development of the economy, its dynamism and potential. More and more the development of production, economy, and society becomes dependent on management. And in management itself great changes take course. The informative possibilities expand; the role of knowledge increases and the problem of knowledge control appears; the personnel becomes the human capital; the amount of alternatives of the problems being solved in the processes of management; management itself transforms into a science and, at the same time, remains a unique skill of the work with people; new requirements are imposed upon managers – the requirements of activity professionalism. In the new century a profession becomes a key stratifying factor.

At the present moment the occupational status of a Russian manager is formed of two moments: the obtained education with its symbolic rating of intellectuality and potentialities (capabilities) – diplomas, and the professionalism properly as an aggregate of experiences, skills, and technologies of organization problems’ solutions.

In the sphere of business-education two basic models - German and American – are being used now. Both of them demonstrate their successfulness in the countries of market economy and are the prototypes of business-education systems generation in other countries. The European or German (traditional) model is based on the separation of higher professional education according economic, engineering, humanitarian schools and managerial personnel development within the system of extended education. Within the framework of the specified model the attention is paid to the “after-experiential education”, which is made up of regular participation of active managers in short-term personnel development programs on topical problems of management. The American (new) model named the “professional manager” is based on the creation of business-schools as general centers of research and

education in the sphere of management. At that, management – is not only a professional activity aspect and an independent science, but also a social layer carrying out the administrative function in the industrial society.

According to the model of business-education a manager as a separate profession is consolidated in different ways in developed nations. It is probable that originally national features of business life formed managers as an independent profession, but currently the management-education system itself must become the factor affecting the further separation of managers as professionals.

In the analytic reference book “Business-education in Russia” (1998) a shot at describing national models of managers’ training in developed countries on the following characteristics was made: recognition of management as a profession, basic education, possibility of getting Master’s degree, research in the field of management, availability of quality educational materials, forms of mastering the profession of a manager, creation of Educational Centers in organizations, development of professional culture and socialization. There is no analogous description for the Russian national model and its absence doesn’t allow carrying out the quality training of Russian managers.

In business-education the American model might be the only deep-laid one, where management is considered as a profession. In the rest of the models there is a great opposition to the fact that a manager is a profession. Management in Russia, Germany, France is perceived as a certain topside to a profession, for example, manager-engineer and manager-economist. Though, some advances of the American economy testify that the professionalizing of management improves the efficiency of an organization activity greatly and, in terms of the social aspect, promotes the professional dynamics of specialists.

In the former Soviet Union the ideas of management development, the use of managerial economics among them, became urgent in the 60s. Finally, the development of these ideas has led to the comprehension of the managerial professionalizing necessity and this area specialists’ training concepts formulation. The most complete expression and practical importance this concept got at the beginning of the 80s. At that time the specialty “Management” with a number of branch, functional and problem specializations was opened. Further a whole complex of management-education specialties appeared: marketing, human resource management, information management and others. At the present time 485 higher colleges in Russia perform their training, but according to specialists’ calculations they are able to satisfy business wants for 38%.

From the outset of managers’ professional training organization in Russia some of its branches were developed: first education, extended education,

later on – second education, professional development, reeducation. These branches didn't come between each other, but, vice versa, enriched the topics and managers' training methods. The first education was the leading one, as within the framework of its development a fundamental approach to professionalism, management efficiency and issue analysis methods were formed. The extended education characterized practical want of knowledge and a set of the most burning problems of management development.

The experience of the USSR and Russia in managers' training organization can be estimated in different ways. In the USSR there was planned and directive economy and, therefore, the training of specialists in the field of management until the 90s disagree with present-day wants of the market system. Partly this statement is correct. However, many problems of large industrial branches and complexes administration remain urgent nowadays, as well. The formation of large-scale and fundamental thinking of the manager – is also the experience of managers' training development in Russia. The ability to solve organization problems not always depends on socio-economic administrative conditions. And these abilities were also projected in the previous stages of managers' training development in Russia. It is of paramount importance that in the short period of economic conversions from the 90s up to the present moment Russia has obtained and accumulated a unique experience of managerial professionalism. And this circumstance is impossible to be ignored while discussing the problem of managers' training.

The stratification structure changes: dynamic processes in occupational groups are traced, new professions and kinds of activity come into being. The possibilities of management-education in Russia are widely discussed. Many research workers hold by the opinion that the expansion of management-education is closely connected with professionalism and national managerial positions formation. Mastering the profession of a manager becomes the source of an individual's recruitment into a new socio-economic field. At the same time the economical branches and concrete

enterprises are in acute want of professional managers. In accord with the RF President Edict № 774 of 23.07.1997 the "Program of management training for the RF national economy organizations" has been realized, the realization of which being dealt by 81 regional branches and 102 Russian higher colleges and syndicates being engaged. The strategic target of the program is to create a reserve of highly skilled competent managers and the formation of management potential able to provide the development of all economical branches enterprises in Russia. The most important of these management tendencies is the managerial activity professionalism, professional managers' training, and creation of conditions for their professional activity.

The educational situation on managers' training still remains indefinite, as in the Russian society the social mandate for managers has not been formed, and the activity of educational establishments on managers' training reminds an experiment. The independent forms and mechanisms of employers' and occupational communities' participation in solving the problems of educational policy, including the processes of independent social quality rating of management-education, has not been developed enough. The weak integration of educational, scientific and productive activities can lead to the ultimate separation of theory from practice. The content of management-education and educational technologies still remain inadequate to the up-to-date requirements and tasks of Russian education competitiveness provision in the world's market of educational services.

It should be noted that the discussed above allows defining the subject matter of management investigation, emphasizing national models of managers' training and the evolution of views on professional training of managers.

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*Materials of conference***APPLICATION PHITOPROBIOTICS AND POLYSALTS OF MICROCELLS IN ANIMAL INDUSTRIES**

Nikolayeva O. N., Mjuristaya M. L., Andreeva A. V.
The Bashkir State Agrarian University, Ufa, Russia

Advantages and opportunities of development of animal industries are limited to a lot of factors, one of which are gastroenteric diseases of animal early postnatal period noncontagious etiology. Therefore the problem of searching new medicines which are influential on immune functions of the organism is actual. These medicines are helpful in adaptation mechanisms of newborn animals to a new inhabitancy. For this purpose we approve compositions phitoprotiotics and polysalt microcells. Phitoprotiotic is a complex preparation on the basis of a probiotic lactobacterin and prebiotic (water extraction of a grassy part of plants, stabilized in a nutrient medium on the basis of dairy whey). Polysalt of microcells is a complex of copper and zinc

Efficiency of the preparations tested in conditions of the state farm-factory «Dmitrievskij» (republic Bashkortostan) on 56 newborn calves black-motley breed and 56 pigs one month old of large white breed. Animals by a principle of analogues have been divided into 7 groups on 8 heads in everyone (1 control and 6 skilled). Calves and pigs of the 1-st control group contained in usual conditions. First skilled group (the control of polysalt) with a forage received polysalt - 50 mg on a head (calves) and 120 mg on a head (pigs) within 30 days; second skilled group (the control lactobacillus) - «Alive weight lactobacillus» with the first portion of colostral milk (calves) daily on 20 ml and with water on 8 ml (pigs) daily due 10 days with an interval in 10 days within 1 month; for calves and to pigs of the third skilled group feeded under the same scheme «Alive weight lactobacillus on a nutrient medium with addition of lucerne of 2%»

and polysalt of microcells; to the 4-th skilled group feeded «Alive weight lactobacillus on a nutrient medium with addition of 3% of a celandine» and polysalt of microcells; to the 5-th skilled group - «Alive weight lactobacillus on a nutrient medium with addition of a barberry of 4%» and polysalt of microcells; to the sixth skilled group - «Alive weight lactobacillus on a nutrient medium with addition of a barberry of 2% and 1% of lucerne» and polysalt of microcells.

Efficiency of preventive maintenance of gastroenteric diseases of the calves above-named compositions of preparations in skilled groups has made 87,5-100%, whereas in the control-50%. At control animals attributes of the gastroenterit disease appeared for 2 days, and illness, despite of undertaken intensive treatment by traditional preparations, last 7-8 days. Calves of skilled group, as a rule, fell ill on 3-4 day of living and recovered on 4-5th days. The daily average gain of the experimental calves was on the average 587-633 gr., whereas at analogues of the control-458 gr. Compositions of phitoprotiotics with polysalt of microcells have allowed to increase daily average additional weights of pigs on 209-220 gr., whereas in the control they have made 194 gr. Average duration of illness at pigs control group were during 5-6 days, and animals of skilled group recovered already on 3-4th days. Safety of pigs one in all groups has made 100%.

Thus, use of compositions of phitoprotiotics and polysalts of microcells provides the expressed preventive effect at gastroenteric diseases on a young growth of animals noncontagious etiology.

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Materials of conference

ONE POSTULATE – AND MERE MEMORY
REMAINS FROM INERTIAL FORCE

Rostovtsev A.K.
Kamyshin, Russia

“The laws of Physics must have one and the same form for all the observers, including those moving with acceleration.”

Albert Einstein

Newton's third law of motion maintain that the forces, with which two bodies affect each other, are equal in modulus and directed to the opposite sides along the straight line connecting these bodies. The forces do not equalize each other:

$$F_1 = -F_2 \quad (1).$$

$$\text{If } F_1 = F_2 = ma \quad (2),$$

where m – is the body's mass, a – is the acceleration, then the equation will be written as follows:

$$ma = -ma \quad (3),$$

$$\text{whence it follows that } a = -a \quad (4).$$

The physical content of the equation (4) is known to the Lord alone, that is why let us give this equation its own physical sense with an introduction of a postulate.

Postulate

Any material point moving with acceleration creates an inert (gravitational) field equal to the acceleration and directed oppositely to it. The inert field, unlike the gravitational one, doesn't interact with material points and bodies.

Newton's laws have been formulated for inertial frames of reference – the systems connected with the bodies, which are affected by the outside forces. Within the systems moving with acceleration these laws fail. To use Newton's laws in noninertial frames of reference it is necessary to take into account that all bodies behave in these systems as if a change of the gravitational field occurred and the free fall acceleration vector nearby the Earth g_0 got an incrementation – a equal to the system's acceleration (in reference to the inertial system) taken opposite in sign. In other words, in noninertial frames of reference located nearby the Earth one can use the same laws, formulas and equations that are used in inertial ones, but everywhere it is necessary to change the vector g_0 with the vector g equal $g = g_0 + (-a)$ (5).

Weight is the force, with which a body, being gravitated to the Earth, affects the bearer or strains the suspension: $P = mg$ (6).

Inserting the equation (5) into the equation (6) we will get: $P = mg + m(-a)$ (7).

If $a = 0$, then the weight is equal to the gravity force: $P = mg_0$ (8).

Let us consider this theory as an example. Let a body with a mass of m is moving in a circle of the radius r at the speed of V . The body is affected by the gravitation force mg_0 and the funicular force T . The resultant of these forces is equal to the centripetal force equal (see Fig.1): $F_{it} = ma$ (9).

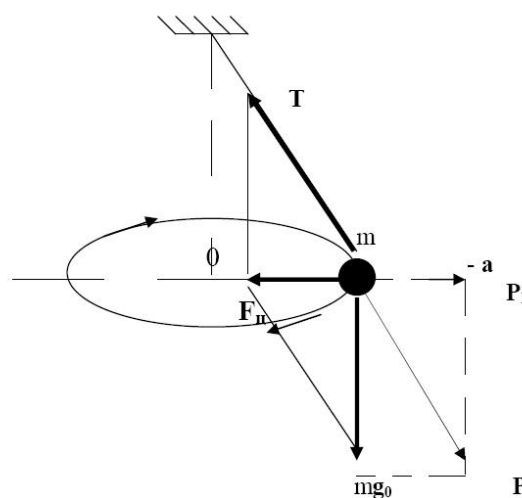


Figure 1.

According to the postulate mass creates an inertial field $-a$. Then the weight of the body will be equal

$P = mg + m(-a)$ (10) and it is attached to the funicle in accordance with Newton's third law of motion and weight metering.

From all the said we resume: Newton's laws are correct both in inertial and noninertial frames of reference.

As for the inertial force, it is substituted by one of the body weight components P_1 .

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