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DISCONTINUATION OF TREATMENT OF SCHIZOPHRENIC PATIENTS IS DRIVEN BY POOR SYMPTOM RESPONSE: A POOLED POST-HOC ANALYSIS OF FOUR ATYPICAL ANTIPSYCHOTIC DRUGS

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Stopping antipsychotic treatment can interrupt improvement and exacerbate the illness. The reasons for discontinuing treatment during controlled clinical trials were analyzed to explore this phenomenon.
A post-hoc, pooled analysis was made of 4 randomized, double-blind clinical trials, 24– 28 weeks in duration, involving 1627 patients with schizophrenia or a related disorder. Analyses combined all the atypical antipsychotic treatment groups in the studies.
The majority of patients (53%) stopped their treatment at an early stage. Poor psychiatric response along with worsening symptoms was the most frequently given reason for discontinuing the course (36%), which was substantially more common than discontinuation due to poor tolerability of the medication (12%). This phenomenon was corroborated by less improvement in patients who discontinued treatment compared with those who completed, based on the PANSS total scores. Discontinuation due to poor response was, apparently, more predominantly linked to patient perception than to physicians' conclusions alone (80% vs. 20%). Discontinuation due to patient perception of poor response appeared to occur particularly early in the course of treatment. Patients who discontinued due to poor toleration of the medication responded in a more comparable manner with completers.
Discontinuing treatment may lead to exacerbation of symptoms, undermining therapeutic progress. In these studies, poor response to treatment and worsening of underlying psychiatric symptoms, and to a lesser extent, intolerability to medication were the primary contributors to treatment being discontinued. Our findings suggest that adherence may be enhanced by effective symptom control, as objectively measured and as subjectively perceived. Such strategies may improve patients' willingness to undertake long-term therapy and increase the likelihood of a better prognosis.

Background

Adherence to a drug regime is a significant issue in the clinical management of schizophrenia. Early treatment discontinuation on the part of patients with schizophrenia or schizophrenia-like disorders is strikingly common, with estimates of its prevalence in antipsychotic drug trials ranging from 25%–75%. The rates of nonadherence appear to be even higher in natural, uncontrolled settings [1 - 4]. The consequences of early termination of the treatment are significant, making adherence to medication a critical determinant of a generally good prognosis. Discontinuing a prescribed antipsychotic drug is associated with symptom exacerbation [5], relapse [5,6], increased hospitalization [5,6], poor long-term course of illness [7], and higher economic costs of treatment [8]. Seventy-five per cent of patients who stop taking their antipsychotic medication experience significant worsening of symptoms over the course of a year compared with only 25% of those who consistently take their medication [5,6].

There are many factors associated with stopping treatment at an early stage. These can be separated into causes, such as:

- treatment-related reasons, e.g. inadequate response and adverse events;
- patient-related reasons, e.g. insight and attitude;
- and environmental elements, e.g. family support and transportation availability [5, 9 ,10].

Adverse effects of treatment are one of the more frequently cited reasons for

noncompliance with antipsy chotic medication [5,9]. A patient's likelihood of adhering to prescribed medication is a product of an implicit and subjective assessment of the relative costs and benefits of adherence in relation to personal goals and constraints [3 ,9, 11].

Recently, cessation of medication has been used as a measure of ineffectiveness in the management of schizophrenia [12- 14]. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial was a large, randomized, controlled trial that evaluated the effectiveness of atypical and conventional antipsychotic medications in patients with schizophrenia over an 18-month period [14]. Its primary variable was the time taken to reach discontinuation of medication, for any reason. In this context, treatment discontinuation reflects in different proportions both patient and clinician views of efficacy and tolerability.

The significant impact of treatment adherence on clinical outcome and the increasing belief that continuation is as a proxy for overall effectiveness make it important for us to understand the reasons why treatment is in many cases discontinued. Randomized, controlled clinical trials may provide information that may help to shed light on what happens under clinical care. We, therefore, undertook a secondary analysis of actively-controlled trials of olanzapine for schizophrenia and schizophrenia-like illnesses to explore the reasons for treatment discontinuation by collapsing all the treatment groups. Our goal was to better understand the roles that efficacy and tolerability play in treatment discontinuation, along with the relative roles of patient and clinician perception.

Methods

Patient population

This was a post-hoc, pooled analysis of clinical trials within the Eli Lilly and Company database. The study selection criteria were 1) randomized, double-blind, active-controlled, 2) duration of 24 to 28 weeks, and 3) schizophrenia, schizophreniform disorder, or schizoaffective disorder. Four studies met these criteria. The 4 studies included 1627 patients treated with olanzapine, risperidone, quetiapine, or ziprasidone. None of the studies included a placebo arm. Patients were men and women between the ages of 18 and 75. All protocols were approved by the ethical review boards responsible for individual study sites. All patients gave written, informed consent prior to entering the study. The pooled analysis included 1 trial comparing olanzapine and risperidone [15], 1 trial comparing olanzapine and quetiapine [16], and 2 trials comparing olanzapine and ziprasidone [17 , 18]. Concomitant psychotropic medications were not allowed during the studies with the exception of limited benzodiazepines / hypnotics, approved antiparkinsonian medications, and in studies 2 and 4, antidepressants if a patient had been on a stable dose for 30 days prior to study enrollment and remained on a stable dose during the study.

Study designs

Study 1 was a 28-week, multi-center study of olanzapine (10–20 mg/day, n = 172) versus risperidone (4–12 mg/ day, n = 167) in inpatients and outpatients meeting diagnostic criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder according to the DSM-IV [15]. Patients had an initial score on the Brief Psychiatric Rating Scale (BPRS) of at least 42.

Study 2 was a 6-month, multicenter study comparing the efficacy of olanzapine (10–20 mg/day, n = 171) with quetiapine (300–700 mg/day, n = 175) in outpatients meeting DSM-IV criteria for schizophrenia and schizoaffective disorder who had poor functioning and prominent negative symptoms [16]. Patients had a score ≤60 on the Global Assessment of Functioning (GAF) and a score ≥4 on at least 3 or ≥5 on at least 2

of the 7 negative scale items on the Positive and Negative Syndrome Scale (PANSS).

Study 3 was a multicenter, 28-week study of olanzapine (10–20 mg/day, n = 277) and ziprasidone (80–160 mg/ day, n = 271) in inpatients or outpatients meeting DSM- IV criteria for schizophrenia [17]. Patients had an initial score of at least 42 on the BPRS and a score ≥4 on 1 of the PANSS positive items in addition to a Clinical Global Impressions-Severity score ≥4.

Study 4 was a multicenter, 24-week, fixed-dose study of olanzapine (10, 15, or 20 mg/day, n = 202) and ziprasidone (80, 120, or 160 mg/day, n = 192) in inpatients or outpatients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder with concurrent depressive symp toms [18]. Patients had a score ≥16 on the Montgomery-Åsberg Depression Rating Scale (MADRS) and ≥4 on Item 2 (reported sadness).

Assessments

The primary objective of the present analysis was to assess the pattern and reasons for treatment discontinuation/ continuation by pooling the 4 studies and collapsing all treatment groups. Clinical trial investigators in all 4 studies were required to record reason and date of discontinuation when patients left the trial before completing the study. A clinical report form with a checklist of potential reasons for discontinuation was used. The reasons for discontinuation are as follows:*1) Adverse Event (AE)*-with the event specified. *2) Entry Criteria Not Met*-checked when a patient had been inappropriately enrolled in the trial based on specific entry criteria. *3) Lack of Efficacy (LOE)-Patient Perception*-the patient perception was that symptom improvement was not adequate for continued use of the randomized medication. *4) Lack of Efficacy (LOE)-Phy-sician Perception*-the physician perception was that symptom improvement was not adequate for continued use of the randomized medication. *5) Lack of Efficacy (LOE)-Patient and Physician Perception*. *6) Lost to Follow-up*-a patient did not come to a scheduled visit and subsequently was unable to be contacted by phone or mail. *7) Noncompliance*-patients intentionally missed all doses for a number of consecutive days specified for each trial or regularly took more than the prescribed amount of medication. *8) Personal Conflict*-the patient's decision for a variety of personal reasons, such as work conflict, lack of transportation, change of location, or unwillingness to fill out questionnaires. *9) Physician Decision*-physician decided that a patient should be discontinued due to reasons other than lack of efficacy or satisfactory response; examples include investigator sites closing and patients deemed unreliable. *10) Sponsor Decision*-the sponsor, Eli Lilly and Company, decided that a patient should be discontinued following consultation with the investigator treating the patient. *11) Clinical Relapse-Study 2 Only*-clinical relapse was based on predefined criteria, including an increase in the following positive symptoms of schizophrenia: delusions, conceptual disorganization, hallucinatory behavior, or suspiciousness as measured by PANSS; an increase in self depreciation as measured by the Calgary Depression Scale for Schizophrenia; or hospitalization for any psychiatric condition. *12) Satisfactory Response-Study 1 and Study 2 Only*.

For the present analysis, discontinuation due to lack of efficacy based on either patient or physician perception (reasons 3, 4, and 5) was grouped together and used as a measure of discontinuation due to poor symptom response to treatment (termed poor response). Discontinuation due to psychiatric adverse events (e.g., emergent psychosis or depression) along with "Clinical Relapse" (Study 2 only-reason 11) was used as a measure of discontinuation due to symptom worsening. These 2 categorizations, poor response and symptom worsening, represent a continuum of treatment inefficacy. In contrast, discontinuation due to non-psychiatric adverse events was considered

discontinuation due to medication intolerability.

The psychopathology of schizophrenia was measured by visitwise analysis of mean total scores on the PANSS [19]. The PANSS is a 30-item scale that was designed to capture numerous symptoms of schizophrenia, including delusions, grandiosity, blunted affect, poor attention, and poor impulse control.

Statistical methods

The analyses in this research were conducted combining all the treatment groups in the 4 clinical studies. The differences in PANSS total scores between study completers and discontinued patients were tested using Analysis of Variance (ANOVA) with term for group (completed vs. discontinued) at all timepoints that were common for all studies (Weeks 2, 4, 6, 8, 16, 20, and 24). In addition, PANSS total scores were also compared among completers and patients who discontinued due to various reasons, such as poor response/symptom worsening, intolerability to medication, and others using ANOVA with term for group. Logistic regression analysis was applied to test if early response predicts study completion with the independent variable as change in PANSS total at Week 2. A similar model was used with the predictor as a categorical variable defined as an improvement of 20% or greater in PANSS total from baseline to 2 weeks.

Data on treatment discontinuation due to poor response (lack of efficacy) were further assessed to compare the patient's role to the physician's role in the perception of treatment ineffectiveness and subsequent discontinuing medication. In order to emphasize patient attitude toward treatment response and the role of the patient in the decision to discontinue treatment, patient perception was based on discontinuation by patient perception of poor response either alone or in consensus with physician perception (reasons 3 and 5) for the purpose of the current analyses. Physician perception was based on physician perception alone (reason 4).

Table 1. Patient and disease characteristics

Characteristic	Study 1 (n = 339)	Study 2 (n = 346)	Study 3 (n = 548)	Study 4 (n = 394)	Total (N = 1627)
Age (mean ± SD)	36.21 ± 10.73	41.05 ± 9.58	39.10 ± 11.8	41.59 ± 9.74	39.53 ± 10.85
Sex (Male %)	220(64.9)	228(65.9)	352(64.2)	248(62.9)	1048(64.4)
Race (Caucasian %)	253(74.6)	179(51.7)	239(43.6)	197(50.0)	868(53.3)
Diagnosis (%)					
Schizophrenia	277(81.7)	230(66.5)	548(100)	223(56.6)	1278(78.5)
Schizoaffective	52(15.3)	116(33.5)		171(43.4)	339(20.84)
Schizophreniform	10(2.9)				10(0.6)
Age of Onset Illness (yrs ± SD)	23.51 ± 7.48	23.36 ± 8.21	23.37 ± 8.27	23.71 ± 8.93	23.48 ± 8.26
PANSS Total (mean ± SD)	96.08 ± 16.55	84.83 ± 14.03	100.9 ± 20.18	79.35 ± 17.51	91.27 ± 19.72
Prior Hospitalization (%)	337(99.4)	180(52.0)	105(19.2)	189(48.0)	811(49.8)
Hospitalization Days (mean ± SD)*	23.12 ± 43.89	55.45 ± 77.13	16.10 ± 37.4	41.12 ± 44.10	33.58 ± 54.31
Illness Duration (yrs ± SD)	12.57 ± 9.75	17.68 ± 9.50	15.80 ± 11.63	17.84 ± 10.59	16.02 ± 10.75

* Mean hospitalization days for group of patients reporting prior hospitalization.

It should be noted that results regarding perception would differ if patients that discontinued due to poor response based on the consensus of both patient and physician perception were categorized differently. Time to discontinuation due to poor response was assessed by Kaplan-Meier estimators for patient perception and physician perception.

Clinical response as measured by PANSS total scores were compared between patient perception and physician perception at all available visits using ANOVA. For patients who discontinued due to adverse events, the actual event was identified for all but 6 patients. All statistical tests are based on a 2-tailed significance level of .05.

Results

Table 1 summarizes the study sample at baseline across the 4 studies with treatment groups combined. A majority of patients were male (64.4%), Caucasian (53.3%), and had a diagnosis of schizophrenia (78.5%). The patient mean age was 39.5 ± 10.8 years, and the mean age of illness onset was 23.5 ± 8.3 years. The mean baseline PANSS total score was 91.27 ± 19.72, and 49.8% of patients had been hospitalized prior to the study.

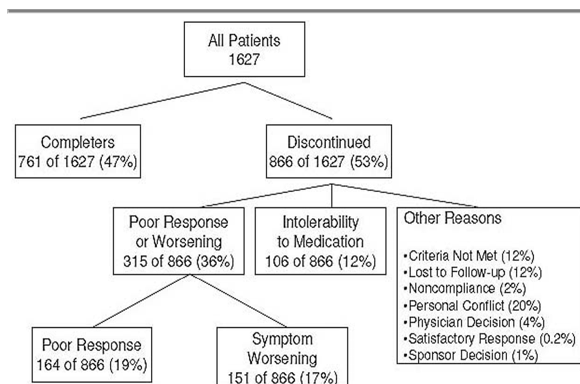

Figure 1. Flowchart of early treatment discontinuation. Values are the summary of reasons for discontinuation from all 4 studies. Poor Response was based on "Lack of Efficacy." Symptom Worsening was based on "Psychiatric Adverse Events" and *a priori* protocol defined "Clinical Relapse" (Study 2 only).

Reasons for discontinuation

A majority of patients (53%; 866/1627) discontinued early from these 4 studies. The reasons for discontinua tion are summarized in Figure 1. The most common rea son for early treatment discontinuation was poor response/psychiatric symptom worsening (36%; 315/ 866), which was 3 times the rate of patient discontinuation due to medication intolerability (12%; 106/866). In particular, poor response accounted for 19% (164/866) of patient discontinuation, and symptom worsening accounted for 17% (151/866). The most common psychiatric adverse events (symptom worsening) cited for treatment discontinuation were psychosis (n = 35); suicide ideation, attempts, or completion (n = 18); schizophrenia, schizoaffective, or schizophreniform disorder (n = 17); and depression (n = 12). The non-psychiatric adverse events (medication intolerability) most frequently cited for treatment discontinuation were sedation (n = 7), somnolence (n = 7), abnormal ECG (n = 6), vomiting (n = 5), dizziness (n = 4), dystonia (n = 3), fatigue (n = 3), abnormal liver function test (n = 3), and increased weight (n = 3). The rates of and reasons for discontinuation across the 4 studies were fairly consistent and are shown in Table 2.

Symptom response: Completers versus patients who discontinued

In order to objectively examine the association between poor clinical outcome and treatment discontinuation independently of the checklist used at patient departure, PANSS total scores at each assessment were compared between patients who completed the study and those who discontinued early.

Table 2. Reasons for discontinuation by study

Reason for Discontinuation n (%)	Study 1 (n = 339)	Study 2 (n = 346)	Study 3 (n = 548)	Study 4 (n = 394)	Total (N = 1627)
Overall Discontinuation	161(47.5)	190(54.9)	268(48.9)	247(62.7)	866(53.2)
Poor Response or Worsening Intolerability to Medication Other Reasons*	67(41.6) 19(11.8) 75(46.6)	78(41.0) 16(8.4) 96(50.5)	99(36.9) 31(11.6) 138(51.5)	71(28.7) 40(16.2) 136(55.1)	315(36.4) 106(12.2) 445(51.4)

*Other reasons for discontinuation included criteria not met, lost to follow-up, noncompliance, personal conflict, physician decision, satisfactory response, and sponsor decision.

There was no significant difference in baseline PANSS total scores between the patients who completed and those who discontinued treatment (91.4 ± 19.2 and 91.1 ± 20.2, respectively; $p = .744$). However, at each timepoint after treatment had begun, patients who completed the study had significantly lower PANSS total scores than patients who discontinued prior to the end of the study ($p < .001$, Figure 2). Although both groups showed significant clinical improvement compared to baseline ($p < .001$ at each timepoint), patients who discontinued early from the study appeared to have a slower initial rate of improvement and less improvement overall as compared to those patients who completed the study.

In view of these results, it was of interest to determine if early response predicted study completion. Symptom improvement from baseline to 2 weeks as measured by mean change in PANSS total score was significantly predictive of study completion (regression coefficient estimate 0.02, $p < .001$). Further, defining early response as a 20% or greater improvement in PANSS total score at 2 weeks, 28.9% of patients (431 of 1492 available at Week 2) met the criteria. Based on this criteria, early response was associated with an approximately 80% greater likelihood of completing the study (odds ratio 1.76, confidence interval 1.4, 2.21, $p < .0001$).

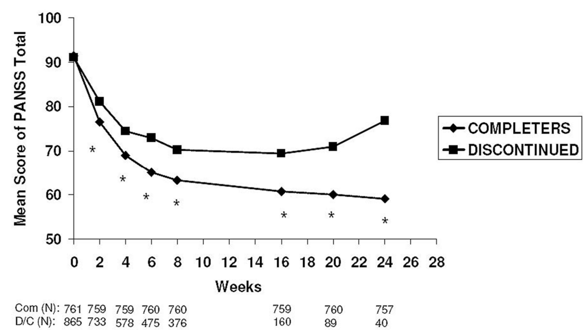

Figure 2. Visitwise PANSS total scores between patients who completed the study and those who discontinued early. Values are means across all treatments and studies. *$p < .001$ between group difference. Completers (Com), Dis-continued (D/C).

PANSS total scores at each assessment were also compared among completers and patients who discontinued treatment early due to poor response/symptom worsening, intolerability to medication, and "other," respectively. "Other" reasons for discontinuation were the same as those described in Figure 1 and as described in detail in the Methods section. There was a cross-group significant difference from Week 0 through Week 6 and also at Week 20 ($p < .05$; Figure 3). In contrast to patients who discon tinued due to poor response or symptom worsening, patients who discontinued due to medication intolerability showed improvement in PANSS total scores comparable to study completers, suggesting that adverse events do not interfere with symptom response but do prevent an otherwise effective treatment.

The baseline characteristics of patients who discontinued early due to poor response or symptom worsening are described in Table 3. This group of patients reported prior hospitalization significantly more frequently than all other patients (56.8%; 179/315 vs. 48.2%; 632/1312; p = .007). In addition, these patients were significantly more often Caucasian when compared with all other patients (64.4%; 203/315 vs. 50.7%; 665/1312; p < .001). Other baseline characteristics were similar between patients who discontinued due to poor response or symptom worsening and the rest of the study population.

Patient perception

Discontinuation due to poor response was further characterized to determine whether the patient or physician concluded that symptom response was not adequate for medication continuation. In order to emphasize the role of patients in the decision to discontinue, discontinuation due to patient perception of poor response in the following analyses was defined as discontinuation due to patient perception of poor response (lack of efficacy) either alone or in consensus with physician conclusion. Physician perception was based on physician perception of poor response alone. Patient perception accounted for 80% (132/164) of discontinuation of treatment due to poor response (Table 4 and Figure 4A). In addition, the time to discontinuation was much sooner when patient perception in comparison to physician perception of poor response was the reason for discontinuation (Figure 4B). However, when PANSS total scores were compared between the groups that discontinued due to poor response by patient perception and by physician perception, the clinical performance was similar between the 2 groups (Figure 4C; the only significant difference in PANSS scores between the groups was at Week 4, p = .02).

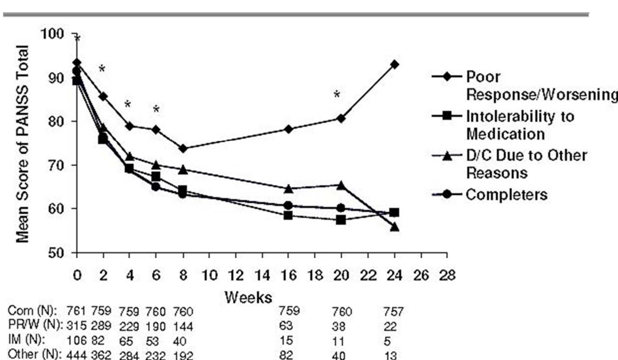

Figure 3. Visitwise PANSS total scores between patients who completed the study and those who discontinued early due to various reasons. Values are means across all treatments and studies. *p < .05 between group difference. Completers (Com), Poor response/symptom worsening (PR/ W), Intolerability to Medication (IM).

Discussion

Premature treatment discontinuation was very common in these 4 schizophrenia clinical trials. The most common reason for early treatment discontinuation was poor symptom response/psychiatric symptom worsening, which was substantially more common than discontinuation due to medication intolerability. Patients who discontinued early from the study due to poor response or symptom worsening had a slower initial rate of improvement and less improvement overall compared to those patients who completed the study. In contrast, patients who discontinued due to medication intolerability were showing symptom improvement comparable to study completers up until discontinuation. Discontinuation due to poor response was overwhelmingly linked to patient perception of response compared to physician observation alone. Discontinuation due to patient perception of poor response appeared to occur particularly early in the treatment course.

The substantial rate of premature discontinuation from these studies likely reflects the great challenge of treatment adherence in the clinical treatment of patients with schizophrenia. Discontinuation by more than half of the patients in these trials is

within the broad range of previous reports of antipsychotic discontinuation (25%–75%) and is in line with reports of medication adherence in nat uralistic settings [1-4]. Both the present study and other analyses of clinical trials likely underestimate the true incidence (and likely the associated burden) of antipsychotic nonadherence in the long-term course of therapy since the studies are time-limited, and treatment of schizophrenia is a life-long consideration. Studies of older typical antipsychotics indicate that about 75% of patients discontinue their medication within 2 years [5].

Perhaps the most interesting and important result of our analysis is that treatment discontinuation due to inadequate control of psychiatric symptoms appeared 3 times as likely as discontinuation due to medication intolerability. This was an unexpected finding of this systematic study since adverse events are a commonly cited reason for medication nonadherence [5,9].

Table 3. Baseline characteristics of patients who discontinued due to poor response or symptom worsening

Characteristic	Study 1 (n = 67)	Study 2 (n = 78)	Study 3 (n = 99)	Study 4 (n = 71)	Total (N = 315)
Age (mean ± SD)	36.17 ± 11.14	39.56 ± 9.36	38.58 ± 11.95	41.77 ± 9.91	**39.03 ± 10.84**
Sex (Male %)	43(64.2)	57(73.1)	58(58.6)	53(74.6)	**211(67.0)**
Race (Caucasian %)*	54(80.6)	48(61.5)	53(53.5)	48(67.6)	**203(64.4)**
Diagnosis (%)					
Schizophrenia	57(85.1)	54(69.2)	99(100)	39(54.9)	**249(79.8)**
Schizoaffective	8(11.9)	24(30.8)	--	32(45.1)	**64(20.5)**
Schizophreniform	2 (3.0)	--	--	--	**2 (0.6)**
Age of Onset Illness (yrs ± SD)	22.80 ± 6.69	21.63 ± 6.85	22.44 ± 7.62	22.63 ± 7.43	**22.36 ± 7.18**
PANSS Total (mean ± SD)	95.48 ± 15.31	86.60 ± 15.60	105.83 ± 22.04	82.01 ± 16.82	**93.50 ± 20.35**
Prior Hospitalization (%)*	65(97.0)	45(57.7)	27(27.3)	42(59.2)	**179(56.8)**
Hospitalization days (mean ± SD)†	35.75 ± 54.52	73.11 ± 113.67	24.96 ± 69.32	49.14 ± 50.12	**46.66 ± 76.40**
Illness Duration (yrs ± SD)	13.25 ± 10.47	17.93 ± 9.53	16.13 ± 12.02	19.13 ± 10.83	**16.65 ± 10.99**

*Significantly different from all other patients (prior hospitalization, $p = .007$; Caucasian race, $p < .0001$).
† Mean hospitalization days for group of patients reporting prior hospitalization.

Table 4. Discontinuation due to poor response by patient and/or physician perception

Reason for Discontinuation	Study 1	Study 2	Study 3	Study 4	Total
Poor Response by Patient Perception Either Alone or in Consensus With	40(76.9)	18(85.7)	46(80.7)	28(82.4)	132(80.5)
Physician n (%*)					
Poor Response by Patient Perception Alone n (%*)	11(21.2)	9(42.9)	25(43.9)	14(41.2)	59(36.0)
Poor Response by Patient and Physician Perception n (%*)	29(55.8)	9(42.9)	21(36.8)	14(41.2)	73(44.5)
Poor Response by Physician Perception n (%*)	12(23.1)	3(14.3)	11(19.3)	6(17.6)	32(19.5)

*Denominator is the total number of patients that discontinued due to poor symptom response.

Clinician experience with the older typical antipsychotics may be partially responsible for the perception of medication intolerabil ity being a more common reason for antipsychotic treat ment discontinuation. Other studies of patient attitudes toward antipsychotic treatment adherence suggest that adverse events may be important for patient attitudes toward antipsychotic adherence in particular with typical antipsychotics [20]. The transition of treatment of patients with schizophrenia and related disorders from typical to atypical agents over the past 10–15 years may have resulted in a decrease in the incidence of discontinu ation due to adverse events relative to poor efficacy.

The high rate of discontinuation in the present study is consistent with the results of the large, 18-month CATIE trial in which 74% of patients discontinued their assigned antipsychotic medication [14]. Treatment discontinuation because of lack of efficacy (24%) was also more common in the CATIE trial than discontinuation because of medication intolerability (15%), consistent with the studies reported here.

Using an objective rating scale (PANSS), patients who discontinued had less improvement compared to study completers, suggesting that this patient group has a real deficit in medication response. However, even patients who discontinued achieved response to a certain extent, suggesting that there is a critical level of response needed to keep patients on treatment. Patients appeared to be especially likely to give up on treatments that did not provide a rapid therapeutic response, as a 20% early response resulted in an approximately 80% greater likelihood of remaining on therapy. Although the notion that a substantial delay in antipsychotic response is common in the field of psychia try [21], Agid et al. [22] recently reported the results of a meta-analysis of double-blind, controlled trials that suggests antipsychotic response starts within the first week of therapy and accumulates over time. In addition, antipsychotic response within the first week of treatment has been reported to predict response after 6 weeks, at least for haloperidol [23]. The present study expands upon these findings by suggesting that early response also predicts treatment continuation. Therefore, patient perception of efficacy early on in treatment may be a major contributor to engagement in treatment and adherence to the treatment plan.

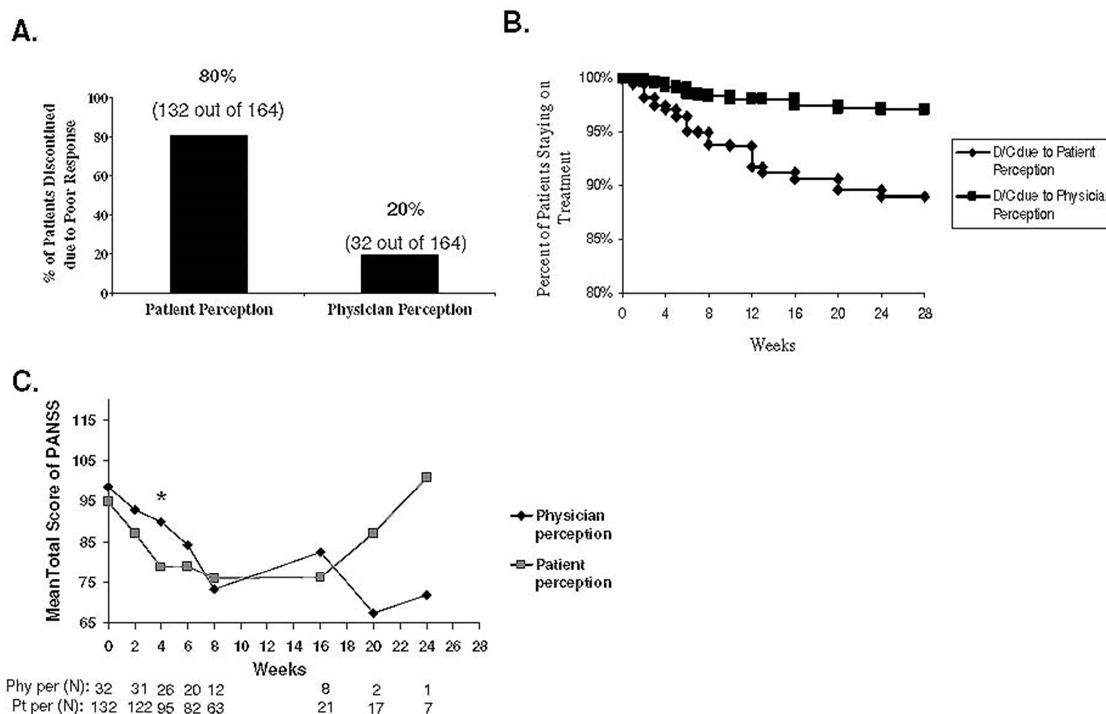

Figure 4. Patient and physician perception of efficacy. A. Discontinuation due to poor response by perception. Patient perception was based on discontinuation by patient perception of poor response either alone or in consensus with physician perception. Physician perception was based on physician conclusion alone. B. Time to discontinuation (D/C) due to poor response by per-ception. C. Visitwise PANSS total scores between patients who discontinued early due to poor response by patient perception and those by physician perception. *p < .05. Physician perception (Phy per), Patient perception (Pt per).

One possible explanation for the inadequate treatment response of patients who discontinued treatment early due to poor response or symptom worsening may be that they are intrinsically less responsive to treatment. For some patients, treatment resistance may represent an intrinsic part of the schizophrenic illness, at least with cur rent antipsychotic medications [24]. The current study provides limited data to address this possibility. In support of this hypothesis, patients who discontinued treatment early due to poor response or symptom worsening reported prior hospitalization significantly more than all other patients. Treatment-resistant patients often require extensive periods of hospitalization, and older studies commonly used frequent hospitalization as an indicator of treatment resistance, although this may not be accurate in all cases [25]. On the other hand, other baseline char acteristics that might be associated with treatment resistance, such as duration of illness and baseline illness severity, were similar between patients who discontinued due to poor response or symptom worsening and the rest of the study population. Standardized criteria for treatment resistance have been more recently described [26 , 27]. Further studies using defined criteria for treatment resistance are needed to better determine if patients who discontinue treatment due to poor response or symptom worsening are truly treatment resistant. Alternatively, these patients may discontinue early because of a suboptimal early treatment response and perceived lack of efficacy, and may possibly benefit from an early, active clinician-initiated attempt to bolster engagement in order to maintain treatment adherence.

Interestingly, patients who discontinued due to medication intolerability were showing symptom improvement comparable to study completers prior to their discontinuation. It should be noted that some of the adverse events were not considered severe; nonetheless, they were costly to patients by derailing patients from the potential benefit of the treatment. Had these patients continued their treatment to study completion, they would have likely had a clinically successful treatment. Therefore, adverse events should be viewed as a significant barrier to treatment efficacy and must be addressed on an individual patient basis.

Weight gain is a potential adverse event of atypical antipsychotic treatment that has been cited by patients as highly distressing [28] and has been proposed to be a fac tor in medication nonadherence [3]. However, weight gain has rarely been directly investigated as a factor in medication discontinuation or adherence. In the present studies, weight gain was infrequently reported as a reason for discontinuation (3 patients; 0.2%). However, weight gain in more naturalistic treatment settings may be a more important factor in patient adherence to medication than reported here for clinical trials. Consistent with this notion, in the CATIE trial, which was designed to have several "real-world" features in order to make the results more generalizable, there was a higher rate of treatment discontinuation due to weight gain than reported here [14]. Four percent of all patients discontinued due to weight gain or metabolic effects, although the incidence of discontinuation due to weight gain or metabolic effects was higher in olanzapine-treated patients (9%).

In addition to the deficit in treatment response as measured by PANSS scores, there was also a subjective component to the poor response reported by some patients. While patient perception of poor response was responsible for treatment discontinuation much more frequently than physician perception of poor response, patients who discontinued due to patient perception of poor response and patients who discontinued due to physician perception of poor response had similar PANSS scores, highlighting a subjective aspect of patient perception of treatment effectiveness. This suggests that

patients are aware of whether they are getting better and may not be as willing as physicians to allow more time for symptom improvement if they perceive early in treatment that their symptom response is less than optimal. These results are consistent with the health belief model that suggests a patient's likelihood of adhering to prescribed medication is a product of an implicit and subjective assessment of the relative costs and benefits of adherence in relation to personal goals and constraints [3, 9 ,11]. These results highlight the importance of active engagement of the patient early in treatment, with a clear understanding of the patient's expectations and treatment goals.

A limitation of the present analysis is that the reasons for discontinuation on the checklist used to categorize discontinuation in the 4 clinical trials may have not optimally captured the primary reason for discontinuation in all cases. For instance, a relatively high number of patients discontinued due to "personal conflicts," which included a variety of specific reasons and were not analyzed in this study. Categorizing all of these reasons as personal conflicts may have prevented the identification of additional barriers to medication adherence and may mask an underlying patient concern regarding efficacy, tolerability, or novel reasons that caused patients to lack the motivation to continue. Finally, discontinuation due to physician perception of response may have been underrepresented since physician versus patient perception was only captured in regards to poor symptom response and was not assessed in regards to symptom worsening (psychiatric adverse events). Although discontinuation due to psychiatric adverse events was ultimately a physician decision, it cannot be concluded that patients did not play a role in this decision. Therefore, discontinuation due to symptom worsening was not considered in the analysis of discontinuation due to patient and physician perception of response.

An additional limitation of the present study is that it is based on clinical trials that may not reflect more naturalistic patient treatment settings. Patients enrolled in the trials were much more homogeneous than the patient population seen in routine clinical care because of restrictions on patient enrollment. For instance, in the trials, patients with alcohol and substance dependence were excluded, and patients generally did not receive polypharmacy. In addition, clinical trials require that patients be motivated to participate in the trial, so these patients may have different implicit motivation and beliefs regarding treatment than patients in other settings. As a consequence, the rates of and reasons for discontinuation reported in this study may not be generalizable to typical outpatient settings. With these caveats, the systematic investigation of reasons for early discontinuation in the present study may still help to develop strategies to improve patient engagement in long-term therapy.

Conclusion

In these studies, as in clinical management of patients with schizophrenia, treatment discontinuation was strikingly common. Poor response to treatment and worsening of underlying psychiatric symptoms, and to a lesser extent, intolerability of medication were the most common reasons for treatment discontinuation. Both a real inadequacy of treatment response, as well as patient perception of failure to improve, contributed to early treatment discontinuation. Improved treatment adherence in schizophrenia can reduce the risk of relapse and its morbid consequences, and perhaps promote higher functioning through better therapeutic engagement and by building upon improvement. This study suggests that adherence may be enhanced by effective symptom control as objectively measured, and as subjectively perceived.

Competing interests

All authors are employees of Eli Lilly and Company.

Authors' contributions

HLS made substantial contributions to the analysis design, data analysis, and critical revision of the manuscript. DHA made substantial contributions to the interpretation of data, drafting, and critical revisions to the manuscript. BJK made substantial contributions to the individual study designs, analysis design, and critical revisions to the manuscript. All authors read and approved the final manuscript.

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REDUCED HIPPOCAMPAL ACTIVATION DURING EPISODIC ENCODING IN MIDDLE-AGED INDIVIDUALS AT GENETIC RISK OF ALZHEIMER'S DISEASE: A CROSS-SECTIONAL STUDY

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The presence of the apolipoprotein E (APOE) ε4 allele is a major risk factor for the development of Alzheimer's disease (AD), and has been associated with metabolic brain changes several years before the onset of typical AD symptoms. Functional MRI (fMRI) is a brain imaging technique that has been used to demonstrate hippocampal activation during measurement of episodic encoding, but the effect of the ε4 allele on hippocampal activation has not been firmly established.
The present study examined the effects of APOE genotype on brain activation patterns in the medial temporal lobe (MTL) during an episodic encoding task using a well-characterized novel item versus familiar item contrast in cognitively normal, middle-aged (mean = 54 years) individuals who had at least one parent with AD.
We found that ε3/4 heterozygotes displayed reduced activation in the hippocampus and MTL compared to ε3/3 homozygotes. There were no significant differences between the groups in age, education or neuropsychological functioning, suggesting that the altered brain activation seen in ε3/4 heterozygotes was not associated with impaired cognitive function. We also found that participants' ability to encode information on a neuropsychological measure of learning was associated with greater activation in the anterior MTL in the ε3/3 homozygotes, but not in the ε3/4 heterozygotes.
Together with previous studies reporting reduced glucose metabolism and AD-related neuropathology, this study provides convergent validity for the idea that the MTL exhibits functional decline associated with the APOE ε4 allele. Importantly, these changes were detected in the absence of meaningful neuropsychological differences between the groups. A focus of ongoing work in this laboratory is to determine if these findings are predictive of subsequent cognitive decline.

Background

Family history of dementia and the apolipoprotein E (APOE) genotype are significant risk factors for the development of Alzheimer's disease (AD). The APOE gene, found on chromosome 19, has three allele variants (i.e., ε2, ε3 and ε4) and six possible genotypes, with the ε3/3 genotype being most prevalent in the general population (but see [1,2]). The presence of the ε4 allele significantly increases the risk and reduces the age of onset in people with the late-onset form of AD, the most common form of this disorder [1,3,4]. Previous studies have reported estimated cumulative lifetime risk percentages based on APOE genotype in individuals with a family-history of AD to be 30%, 46% and 61% for ε3/3 homozygotes, ε3/4 heterozygotes and ε4/4 homozygotes, respectively [5].

Impairment in the encoding and retrieval of episodic memories, presumably caused by neurodegeneration of the hippocampus and other medial temporal lobe (MTL) structures [6,7], is one of the earliest symptoms in AD [8]. Recent evidence suggests that healthy ε4 carriers (mean age = 56 years) with a family history of AD show a greater longitudinal, age-related episodic memory decline than non-carriers [9-11]. Furthermore, some structural MRI studies have found reduced hippocampal volume in

older cognitively normal ε4 carriers [12-16] (but see [17-19]). Taken together, these results suggest that there may be an age-related phenotype for ε4 carriers involving cognitive decline and brain atrophy prior to the onset of AD. An important question is how early these changes occur and whether they can be detected *in vivo* using existing functional imaging methods.

The use of neuropsychological measures and brain imaging to examine cognitively normal individuals with AD risk factors such as family history or APOE genotype could potentially yield valuable information about preclinical alterations in neural function that precede the symptomatic stages of AD. Functional MRI (fMRI) is a non-invasive brain imaging technique that has been used successfully to demonstrate hippocampal and MTL activation during several tasks thought to reflect aspects of episodic memory [20-25]. The few studies that have examined brain activation differences between ε4 carriers and non-carriers have reported inconsistent findings on measures of episodic memory.

One episodic encoding paradigm that has been used to demonstrate robust hippocampal activation is novelty detection, in which individuals discriminate between events that were previously learned from events that are novel [26-31] (see [32,33] for reviews). Tulving and Kroll [34] have suggested that episodic encoding processes are more evident during the processing of novel information versus previously learned (or familiar) information.

Therefore, novelty detection appears to be an important cognitive process involved in MTL-dependent episodic memory formation. Novel/familiar discrimination paradigms might therefore yield valuable information about functional changes in the MTL that precede overt changes in cognitive function in individuals at risk of AD.

The purpose of the present study was to use fMRI to test the hypothesis that cognitively normal ε3/4 heterozygotes with a family history of AD would display reduced activation in the hippocampus during a novel picture-encoding paradigm. We also used voxel-based morphometry (VBM) of T1 weighted images to determine whether any observed differences in fMRI activation between the groups were the result of differences in modulated GM volume. In addition, we compared hippocampal activation against a neuropsychological measure of episodic learning ability. Because prior research has shown that brain changes precede cognitive changes in this population, and because carriers of the ε4 allele may have altered hippocampal function, we hypothesized that there would be less systematic shared variance, disrupting the normal relationship between MTL activation and neuropsychological status in the ε3/4 heterozygotes as compared to ε3/3 homozygotes.

Methods

Subjects

Subjects who enrolled in this fMRI study were grouped by APOE genotype. The statistical analyses included 23 ε3/4 heterozygotes and 17 ε3/3 homozygotes. All participants in the study were recruited from the Wisconsin Registry for Alzheimer's Prevention (WRAP) [35], a longitudinal study designed to identify and evaluate factors that may delay or prevent the onset of AD. This cohort includes cognitively normal adult subjects (total N > 350 participants at the time of enrollment) between the ages of 40 and 65 with at least one biological parent who was diagnosed with AD by physicians affiliated with the Memory Clinics at the University of Wisconsin – Madison. The initial clinical diagnosis of AD in the parent was confirmed using published DSM-IV and NINDS-ADRDA criteria by a diagnostic consensus panel of experienced physicians and neuropsychologists. The adult children of these AD patients were then approached to participate in the WRAP study. The self-reported mean age at onset of memory problems in the parent diagnosed with AD

was reported by the children to be 73 years old (range = 55 – 89 years).

All subjects in the WRAP underwent baseline medical laboratory tests, which included measurements of total non-fasting blood cholesterol, blood pressure, homocysteine, hemoglobin and hematocrit levels, and APOE genotyping. All participants also received detailed neuropsychological evaluations and baseline medical screening that included documentation of current medication usage. An important characteristic of this cohort is that 46% have at least one copy of the ε4 allele [35], compared to approximately 15% in the general population [2,36]. The battery of neuropsychological tests included the following: Wechsler Abbreviated Scale of Intelligence (WASI) verbal and performance IQ indexes [37], Wechsler Adult Intelligence Scale-III (WAIS-III) working memory index [38], the Controlled Oral Word Association Test (COWAT) [39], Rey Auditory Verbal Learning Test (RAVLT) [40], Boston Naming Test (BNT) [41], Trail Making Test A and B [40,42], and the Center for Epidemiological Studies Depression Inventory (CES-D) [43].

WRAP subjects were invited to participate in this fMRI study by direct mailings and newsletters. Subjects expressing interest in participating were contacted by phone and screened to determine if they met study eligibility requirements. The inclusion criteria consisted of the following: no current diagnosis of major psychiatric disease or other major medical conditions (e.g. diabetes, myocardial infarction or recent history of cancer), intact cognitive functions, and MRI scanner compatibility. Of the subjects included in this study, 55% had elevated (> 200 mg/dl) non-fasting total blood cholesterol (10 subjects in the ε3/ 3 group and 12 in the ε3/4 group) and 23% had elevated (> 140 mmHg) systolic blood pressure (5 subjects in the ε3/3 group and 4 in the ε3/4 group). There were no subjects in either groupwith high levels of homocysteine (> 14 µmol/l). Several participants were also taking a variety of medications, 4 subjects were using cholesterol-lowering medications (2 in the ε3/3 group and 2 in the ε3/4 group), 8 female subjects were current users of estrogen replacement therapy (5 in the ε3/4 group and 3 in the ε3/ 3 group), and 6 subjects were using selective serotonin reuptake inhibitors (5 in the ε3/4 group and 1 in the ε3/3 group).

Subjects included in the overall statistical analysis were required to have useable imaging data (movement in the x, y and z planes < 3 mm) and at least 90% accuracy on the fMRI memory task. We restricted our analyses to subjects with a homozygous ε3/3 or heterozygous ε3/4 APOE genotype to reduce the potential genetic variability in brain activation patterns, and because there was an insufficient number of individuals with other APOE genotypes (e.g. ε4/4 homozygotes or ε2/3 heterozygotes) to make meaningful inferencesregarding other APOE genotypes. The data from 6 additional subjects (3 ε3/3 homozygotes and 3 ε3/4 heterozygotes) were excluded from the overall statistical analyses: 1 subject for excessive motion during scanning, 1 subject for scanner error, 3 subjects who did not achieve 90% accuracy on the fMRI task, and 1 subject who had a previously undiagnosed tumor. The final number of subjects included in the statistical analysis was 40 (23 ε3/4 heterozygotes and 17 ε3/3 homozygotes). Athena Diagnostics (Worchester, MA) conducted APOE genotyping for all subjects using their patented procedures.

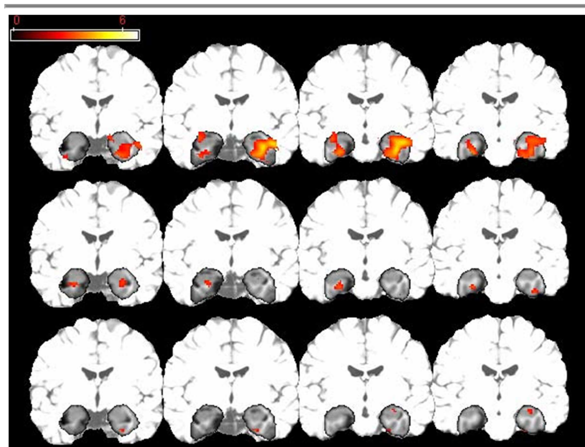

Figure 1. Activation Maps for fMRI task. Statistical parametric maps of the single-group analyses for ε3/3 homozygotes (panel A) and ε3/4 heterozygotes (panel B), and for regions where the ε3/3 homozygotes activated to a greater extent than the ε3/4 heterozygotes (panel C). The left side of each coronal section represents the left hemisphere. The dark-shaded area represents the MTL region to which the statisti-cal analyses were confined. The lighter-shaded areasrepre-sent regions outside of the MTL mask.

fMRI task

Blood oxygen level dependent (BOLD) signal was detected using a variant of a well-known fMRI paradigm in which participants distinguished between novel and previously learned items. This paradigm is well-suited to examining potential differences in hippocampal activation based on APOE genotype because several previous PET and fMRI studies have demonstrated robust hippocampal activation for novel relative to familiar contrasts. The task consisted of serial presentations of line drawings obtained from the Snodgrass and Vanderwart [44] set that were matched for complexity and frequency. The previously learned pictures were presented in a training session 45 minutes prior to the task, and again during scanner setup 15 minutes prior to the task. The items were presented repeatedly in pseudorandom fashion for 15 exposures in each of the two training trials for a total of 30 exposures to each item. The participants were instructed to view the pictures and try to remember them.

During the fMRI test session, pictures were presented continuously at 3 s intervals for the entire experiment. For each picture, the participant decided whether the picture was previously learned or novel. Each picture was presented for 2800 ms with a 200 ms interstimulus interval. The novel pictures (condition 1) were intermixed with the presentation of previously learned pictures (condition 2) using a variable-length block (boxcar) paradigm. There were no periods of rest or fixation during the entire test session. Epoch length was variable, but appropriately balanced between conditions and ranged from single events to 5 consecutive items. The order of condition presentation and length were pseudorandom. Variable-length epochs rather than a fully event-related approach were used to reduce the condition predictability while maintaining some of the statistical power of the boxcar paradigm [45,46]. Two alternate forms of the task were presented (order counterbalanced), using the same previously learned items but different novel items. The duration of the entire task was 9 minutes and 24 seconds. Responses to the novel and previously learned pictures were made with a two-button response device held in the right hand. The index finger was used to identify previously learned pictures, whereas the middle finger was used to identify novel pictures. As in previous studies [see also [31]], we referred to encoding as the contrast of novel relative to familiar pictures.

Imaging procedures

A GE 3.0 Tesla MRI scanner outfitted with an MR-compatible button-box and high-resolution goggles set at 800 . 600 (Resonance Technology; Northridge, CA) were used for fMRI imaging and stimulus presentation.

Table 1. *Demographic, neuropsychological and fMRI task performance data*

	ε3/ε3 (n = 17)	ε3/ε4 (n = 23)
Age (years)	52.1 (6.8)	54.0 (5.6)
Age Range (years)	42 – 65	43 – 65
Education (years)	15.9 (2.1)	16.5 (2.6)
Gender Ratio: Female/Male	11/6	13/10
Handedness (% righthanded)	94%	96%
Homocysteine (μmol/l)	8.2 (1.8)	7.9 (1.5)
Blood Cholesterol (mg/dl) 1	215.8 (32.6)	204.9 (31.4)
Hematocrit (mL/dl)	40.0 (2.1)	40.6 (2.6)
Hemoglobin (g/dl)	13.8 (0.8)	13.9 (0.9)
Systolic Blood Pressure (mmHg)	131.5 (14.1)	132.6 (17.8)
WASI Verbal IQ	112.8 (8.6)	113.6 (10.5)
WASI Performance IQ	114.0 (8.4)	111.9 (8.5)
WAIS-III Working Memory	109.5 (14.5)	104.4 (13.5)
COWAT adjusted raw score	42.8 (10.9)	47.1 (10.0)
Boston Naming Test	56.6 (2.7)	56.6 (1.8)
RAVLT total recall trials 1–5	54.0 (5.2)	52.1 (7.5)
RAVLT short delay recall	11.6 (2.6)	11.0 (2.1)
RAVLT long delay recall	11.7 (2.3)	10.7 (2.9)
RAVLT recognition	14.1 (1.2)	14.0 (1.4)
Trail Making Test A (s)	27.1 (6.0)	27.0 (8.1)
Trail Making Test B (s)	55.4 (19.7)	67.0 (22.3)*
CES-D	4.2 (4.4)	4.1 (4.2)
Snodgrass Accuracy (%)	99.1 (1.2)	98.6 (2.2)
Snodgrass RT (sec)	0.81 (0.2)	0.89 (0.1)
Snodgrass Misses	0.3 (0.8)	0.7 (1.6)

Data are presented as mean (SD). * denotes significant differences ($p < 0.05$) between the groups. WASI = Wechsler Abbreviated Scale of Intelligence, WAIS = Wechsler Adult Intelligence Scale, COWAT = Controlled Oral Word Fluency Test, RAVLT = Rey Auditory Verbal Learning Test, CES-D = Center for Epidemiological Studies – Depression Inventory. See text for further discussion of test measures. 1 = total non-fasting Blood Cholesterol

Foam padding was placed around the head to reduce head motion. The software Presentation http://www.neuro-bs.com was used to deliver visual stimuli and record responses in precise synchrony with slice acquisition and stimulus delivery. A T2*-weighted gradient-echo, echo-planar image (EPI) pulse sequence was obtained with higher order shimming during the functional trials for each subject.

The EPI parameters included: echo time flip angle = 90°; acquisition matrix = 64 . 64 voxels; field of view (FOV) = 240 mm; echo time (TE) = 30 ms; repetition time (TR) = 2000 ms. Thirty sagittal slices of the brain were acquired within the TR at each time point, with a voxel resolution of 3.75 . 3.75 . 4 mm and a 1-mm skip between slices. Over the entire test session, a total of 141 time points were collected. Three images acquired during the first 6 seconds of each scanning run were discarded. Following the functional scans, an axial T1-weighted inversion recovery prepared volume (124 slices; 1.2 mm thick; FOV 240 mm; matrix 256 . 256), and fast recovery fast spin echo T2 weighted anatomic images (TE 90 ms; 70 slices; 1.7 mm thick; 0.3 mm skip; FOV 240; matrix 256 . 256) were acquired. The images were later reviewed by a neuroradiologist for the presence of brain abnormalities that might exclude subjects from the statistical analyses. The T1 weighted images were also used for the VBM analysis.

Table 2. Montreal Neurological Institute (MNI) Coordinates for peak activation differences ($p < 0.01$; uncorrected) for the random-effects group analysis between ε3/4 heterozygotes and ε3/3 homozygotes for the functional MRI encoding contrast of novel versus familiar pictures. k = cluster size

Contrast	Region (k)	Montreal Neurological Institute (MNI) coordinates			Peak t value	P (uncorrected)
		x	y	z		
Novel vs. Familiar						
ε3/3 > ε3/4	Right anterior entorhinal cortex (60)	22	2	-34	3.56	0.001
	- Right parahippocampal gyrus	22	-8	-34	2.99	0.002
	Right hippocampus (93)	30	-14	-16	3.01	0.002
	- Right hippocampus	36	-24	-6	2.99	0.003

Functional image processing

The time series images were motion-corrected to reduce the effects of head movement during the scan session. 3 D field maps across the brain taken co-planar with the fMRI slices were used to correct distortions in the image files by measuring the phase of non-EPI gradient echo images at two echo times (7 and 10 ms). The continuous B field map was estimated using a 3 D phase-unwrapping algorithm based on Jenkinson et al. [47]. Image unwrapping was performed using a nonlinear pixel shifting and B splines interpolation algorithm. The images were then normalized into standard atlas space (using the T2* weighted template from SPM2), written out at a 2 . 2 . 2 voxel resolution, and then smoothed with an 8 mm full-width, half-maximum Gaussian kernel.

Data analysis

Analyses of the time-series data were performed using the General Linear Model using the Statistical Parametric Mapping (SPM2) statistical software [48]. For each participant, the time-series statistical model included convolution with the canonical hemodynamic response function and a high frequency signal filtering (high pass filter = 128 seconds). Temporal autocorrelation was estimated using the first-order autoregressive (AR1) method on suprathreshold voxels. This method estimates the actual autocorrelation from the fMRI time series rather than imposing a generic temporal smoothing filter (see [49] for further discussion).

The primary contrast used to evaluate group differences was novel versus familiar pictures. For completeness, we also examined group differences in activation for the familiar versus novel contrast. All single-subject analyses for both contrasts were computed for each participant and entered into a random effects group analysis. Each of the single-subject analyses was completed in the same semi-automated fashion regardless of APOE genotype. The random-effects group analysis and the correlational analyses were constrained to the right and left MTL, with an anatomical mask described previously by Johnson et al. [50]. The mask extended from the anterior aspect of the amygdala to the posterior aspect of the tail of the hippocampus, and also included the fusiform and parahippocampal gyri (See Figure 1). All possible voxels within each hemisphere of the MTL mask were considered potential dependent variables. The mask was used to impose more stringent hypothesis-driven restrictions on the number of simultaneous comparisons. Uncorrected p-values were used for this restricted region of interest (ROI) approach. In a second step, we conducted whole brain between-group analyses for both contrasts ($p < 0.05$; False Discovery Rate corrected for multiple comparisons) (see [51]).

Voxel-based Morphometry processing steps

The detailed processing methodology for VBM has previously been reported in detail. Briefly, we used the optimized VBM approach described by Good et al. [52] (see also [53,54]) using SPM2. This procedure involves segmentation of the images into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF), and normalization of the GM images to the GM template in standard space. The GM images were then modulated using the Jacobian values derived from spatial normalization and smoothed with a 12 mm isotropic Gaussian kernel. The smoothed GM images were then entered into a random-effects two-sample t-test in SPM2 to examine GM volume differences between the groups.

Results

Neuropsychological functioning and fMRI task performance

The mean scores and standard deviations for the demographic and laboratory test variables and neuropsychological test performance are presented in Table 1. Between-group differences were examined using two-sample t-tests with a Bonferroni-corrected alpha level set at $p < 0.002$ (i.e., $p < 0.05$ divided by 22 comparisons). There were no significant differences between the groups in respect of age, education, laboratory test results or fMRI task performance. Both groups achieved at least 98% accuracy on the fMRI memory task and there were no differences in reaction times. Furthermore, there were no significant differences between the groups in terms of neuropsychological functioning or subjective memory complaints. The two-sample t-tests for each neuropsychological measure revealed no significant differences between the two groups for any of the neuropsychological test measures at the corrected threshold of $p < 0.002$. However, ε3/4 heterozygotes took longer to complete Trail Making Test B than ε3/3 homozygotes, but this finding was only significant using an uncorrected threshold of $p < 0.05$, whereas no significant differences between the groups were found for any of the other test measures. The performances of both groups on Trail Making Test B were within the normal range based on age-matched normative data from Spreen and Strauss (1998), as was performance on the rest of the neuropsychological test battery.

A follow-up analysis that included all WRAP subjects that were ε3/3 homozygotes (n = 154) and ε3/4 heterozygotes (n = 142), including those who did not participate in the fMRI study, revealed no significant difference on Trails Making Test B or any of the other neuropsychological measures. Therefore, the significantly slower time to complete Trails B in the ε3/4 heterozygotes who participated in the fMRI study does not appear to generalize to the WRAP cohort overall, and does not appear to be a general effect of the APOE ε4 allele.

Imaging results

Figure 1 depicts MTL activation for the novel versus familiar contrast in the ε3/3 homozygotes and ε3/4 heterozygotes separately. The ε3/3 homozygotes show a greater level of activation for the novel versus familiar contrast in the MTL including the hippocampus compared to the ε3/ 4 heterozygotes.

The single group analyses provide a qualitative description of differences in MTL activation between ε3/4 heterozygotes and ε3/3 homozygotes. To determine whether there were significant differences between the groups, a random-effects 2-group t-test (with age as a covariate) for the novel versus familiar contrast was performed in the MTL ROI. There was a significant main effect of APOE genotype (x, y, z: 30, -14, -16; $t = 3.01$, $p=0.002$, uncorrected) with ε3/4 heterozygotes showing less activation for the novel versus familiar pictures contrast in the MTL than the ε3/3 homozygotes (see Figure 1).

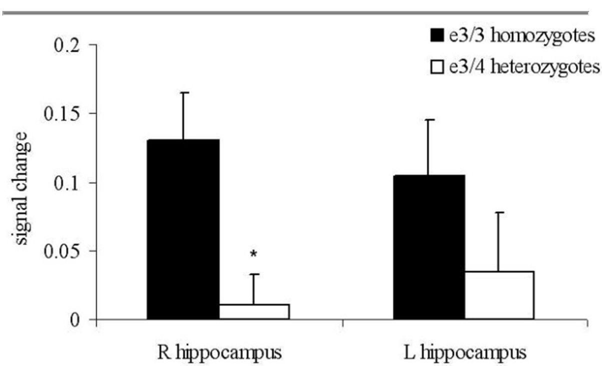

Figure 2. Graph of signal change in the MTL. Plot of the signal change (adjusted fitted responses) for ε3/3 homozygotes and ε3/4 heterozygotes averaged over a 2 mm radius spherical ROI at the local maxima in the right hippocampus (*x, y, z*: 30, -14, -16), and at the same location in the left hippocampus (*x, y, z*: -30, -14, -16). Data are presented as mean signalchange for each group. Error bars represent the standard error of the mean. * denotes significant difference between the two groups.

A plot of the mean signal change averaged over a 2 mm radius sphere in the hippocampus depicts the group difference (*x, y, z*: 30, -14, -16; see Figure 2). For completeness, we extracted mean signal change at the same location in the left hippocampus, and the ε3/3 homozygotes displayed numerically but not significantly (p > 0.25) greater signal change in the left hippocampus as well (see Figure 2). Table 2 provides statistics, locations and cluster size for all significantly activated regions for the genotype effect. There were no significant differences in MTL activation for the contrast of familiar relative to novel pictures.

The whole brain analyses for the novel vs familiar and familiar vs novel contrasts (p < 0.05; FDR corrected for multiple comparisons) revealed no significant differences between the groups for either contrast. In order to examine potential compensatory activity in the cortical regions of ε3/4 heterozygotes, we conducted a follow-up analysis (p < 0.01, uncorrected) using a two-sample t-test in which the analysis was constrained to include only those regions that were active for each contrast (i.e. novel versus familiar or familiar versus novel) collapsed across all 40 subjects (i.e. a one-sample t-test). In addition to reduced MTL activation, the ε3/4 heterozygotes also displayed reduced activation compared to the ε3/3 homozygotes for the novel versus familiar contrast in the right ventral temporal cortex and left parietal cortex.

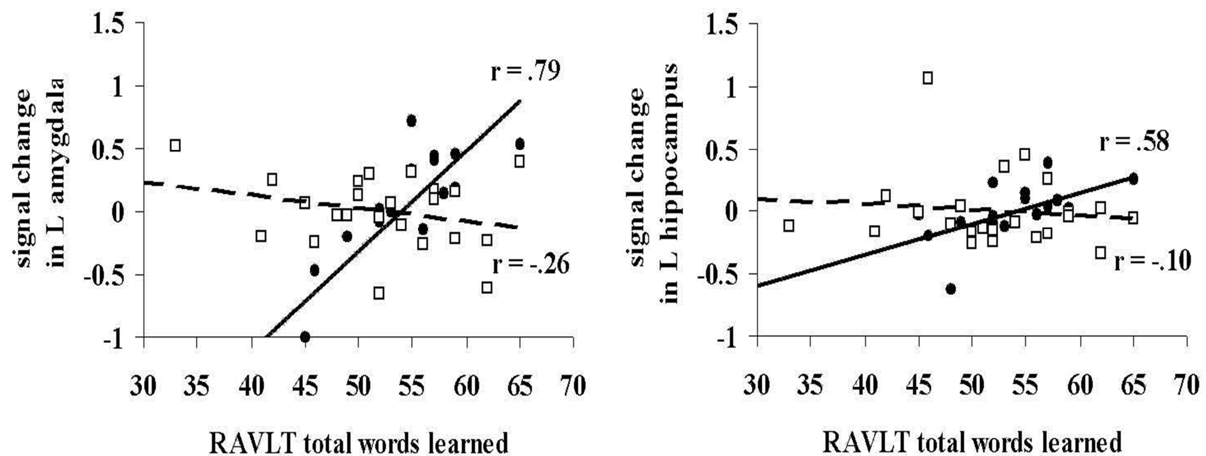

Figure 3. RAVLT versus Signal Change. Scatter plot of the association between total words learned on the RAVLT and signal change within the left amygdala (left panel) and left anterior hippocampus (right panel) for ε3/3 homozygotes (black circles, solid lines)and ε3/4 heterozygotes (white squares, hashed lines).

Importantly, the ε3/4 heterozygotes did not display greater activation compared to the ε3/3 homozygotes in any brain region even at the uncorrected threshold of $p < 0.01$. There were no differences between the groups for the familiar versus novel contrast.

To determine whether the significantly greater MTL activation displayed by the ε3/3 homozygotes relative to the ε3/ 4 heterozygotes was attributable todifferential MTL atrophy, we used VBM analysis [53] of the T1 weighted scans restricted to the MTL anatomical mask in these same participants. This analysis revealed no significant differences in modulated GM volume between the ε3/3 homozygotes and ε3/4 heterozygotes even at a threshold of $p < 0.05$, uncorrected. The absence of differential MTL atrophy indicates that the observed differences in fMRI activation were not attributable to GM volume differences in this group of subjects.

Relationship between RAVLT and MTL activation

We also examined whether the total number of words learned on the RAVLT was associated with fMRI activation in the MTL for the novel relative to previously learned pictures contrast in ε3/4 heterozygotes and ε3/3 homozygotes. Since RAVLT variables are highly correlated, we chose to use total words recalled on the RAVLT because this measure has previously been shown to be sensitive to the preclinical detection of early AD [55]. These analyses revealed that total words learned on the RAVLT was positively associated (see Figure 3) with increased activation in the left anterior hippocampus (*x, y, z*: -28, -6, -26; $r = 0.58$; $p < 0.01$), and the left amygdala (*x, y, z*: -38, 4, -26; $r = 0.78$; $p < 0.0001$) in the ε3/3 homozygotes, but was not significantly associated with activation in the MTL in ε3/4 heterozygotes (r values = -0.26 and -0.10 for left amygdala and hippocampus, respectively). Furthermore, the magnitude of the correlations was significantly different between the two groups for both the left amygdala ($p < 0.0001$) and hippocampus ($p = 0.01$). In contrast, RAVLT total word recall was associated with activation in the left (*x, y, z*: -12, -38, 12; $r = 0.65$, $p < 0.0001$) and right (*x, y, z*: 4, -40, 4; $r = 0.65$, $p < 0.0001$) isthmus of the cingulate cortex in ε3/4 heterozygotes.

For completeness, we also determined the association between RAVLT total word recall and signal at the same coordinates in the right amygdala and hippocampus. These analyses failed to reveal a significant correlation between RAVLT total word recall and signal change in the right amygdala or hippocampus of the ε3/3 homozygotes (*r* values = 0.03 and 0.11 for the right amygdala and hippocampus, respectively) or the ε3/4 heterozygotes (*r* values = 0.19 and 0.11, for the right amygdala and hippocampus, respectively).

Discussion

The present study examined the effects of APOE genotype on brain activation patterns in the MTL during an episodic encoding task in cognitively normal individuals with a family history of AD who were on average 15–20 years younger than the age at which AD symptoms typically develop. We found that ε3/4 heterozygotes displayed reduced fMRI activation compared to ε3/3 homozygotes in the right hippocampus and entorhinal cortex for the contrast of novel relative to familiar pictures. Importantly, there were no fMRI activation differences between the groups for the reverse contrast (i.e. familiar relative to novel), suggesting that the reduced activation found in the right hippocampus and MTL of ε3/4 heterozygotes was not caused by greater fMRI activation to the previously learned items in the ε3/4 heterozygotes, at least when measured relative to novel items. In subsequent whole-brain analyses, no brain regions were found to display greater activity in the ε3/4 heterozygotes than in the ε3/3 homozygotes for either contrast.

There were also no significant differences between the groups in age,

education or memory function, and neuropsychological performance was within the normal range for both groups. This suggests that the reduced MTL activation to novel items (relative to familiar items) in ε3/4 heterozygotes was not caused by impaired cognitive function, and that the observed neurobiological changes in MTL function precede the onset of measurable decline in cognitive function.

We also found no evidence for differences in regional GM volume as measured by VBM, suggesting that the observed activation differences were not caused by reduced MTL GM volume in our cohort of middle-aged subjects. Previous volumetric studies have reported inconsistent findings regarding the effects of the ε4 allele on regional brain volume. Reiman et al. [56] reported nonsignificant trends towards smaller left and right hippocampal volumes in ε4/4 homozygotes (mean age = 58 years), and smaller hippocampal volumes were associated with reduced long-term memory ability. Den Heijer et al. [13] found that elderly ε4 carriers (mean age = 72 years) displayed significantly greater hippocampal and amygdalar atrophy and poorer memory ability relative to ε3/3 homozygotes. Moffat et al. [15] found that older ε4 carriers (mean age = 69 years) displayed a significantly greater rate of hippocampal volume loss over a 3-year follow-up period, although ε4 carriers were also found to display mild decline in memory ability over the same time frame. In a recent large-scale (N = 750) VBM study, Lemaitre et al. [14] found significantly reduced MTL (including hippocampus) volume in elderly (age range 63–75 years) ε4/4 homozygotes compared to both ε3/4 heterozygotes and non-carriers, whereas no significant differences were found between the ε3/4 heterozygotes and the non-carriers. Furthermore, these authors also found that the relative risk of cognitive impairment over a 4-year follow-up period was substantially greater in ε4/4 homozygotes relative to both ε3/4 heterozygotes and non-carriers. Other studies have also failed to demonstrate reduced regional brain volume in ε4 carriers [17-19]. The results of the present study are consistent with these findings.

Since the risk of memory impairment and AD is significantly greater in elderly ε4 carriers relative to non-carriers and younger ε4 carriers [57], cognitive status and age might interact with regional changes in brain volume. Therefore, it is quite possible that the MTL volume reductions found by previous studies in elderly populations were caused by the inclusion of APOE ε4 carriers who were more likely to be in the early stages of AD relative to non-carriers. This interpretation is supported by the findings of previous studies that reduced MTL volume in ε4 carriers was associated with poorer memory performance and increased risk for AD. In any case, the results of the present study failed to demonstrate significant differences in regional GM volume in middle-aged APOE ε3/4 heterozygotes, further supporting the notion that reduced fMRI activation in ε3/4 heterozygotes preceded overt changes in hippocampal volume. More studies are needed to determine the conditions under which the APOE ε4 allele results in reduced MTL volume.

In the present study, we also found that greater encoding ability on a neuropsychological measure of learning (i.e. RAVLT) was positively associated with fMRI activation in the left anterior MTL in the ε3/3 homozygotes but not in the ε3/4 heterozygotes. This signifies that among the non-carriers (in whom the MTL is presumably more intact) the strength of the MTL response was closely matched with better learning ability, whereas among the ε3/4 heterozygotes this relationship was disrupted. The amygdala and anterior hippocampus relationships found in ε3/3 homozygotes are consistent with a facilitative role for the amygdala in processing novel episodic information [58]. There was no

significant difference in the magnitude of the correlations in the amygdala and hippocampus of the ε3/3 homozygotes, so conclusions regarding any differential contribution of these regions to encoding ability are limited. Future studies examining amygdala-hippocampal connectivity during encoding, as well as psychological factors (e.g. context, affective valence) that may modulate neural activity in these regions would be required to determine the role of the amygdala in encoding of novel visual information in people at risk of AD. Nevertheless, this finding does suggest that the left anterior MTL was recruited to a greater extent in ε3/3 homozygotes, whereas ε3/4 heterozygotes with better encodingability may have used encoding strategies that did not actively involve the anterior MTL. The fact that the correlation was found in the left hemisphere in ε3/3 homozygotes is consistent with previous studies that have reported primarily left MTL activation for encoding of verbal material (see [59] for review but see also [60]), suggesting that subjects with greater activation may have used a verbal encoding strategy. In contrast, previous studies in cognitively healthy young individuals (mean age = 30) have reported correlations between memory ability and right hippocampal signal change [60]. The exact reason for the divergent findings is not known. More studies examining correlations between memory ability and fMRI signal change in the left and right hippocampus during episodic encoding are needed to clarify these findings.

To date, six studies have examined brain activation differences between ε3/3 homozygotes and ε4 carriers using fMRI, but only two of these used an activation task that had an episodic encoding component. In a series of studies, Smith et al. [61-63] compared fMRI activation between a group of cognitively healthy subjects with a high risk of AD (i.e. ε4 carriers with a family history of AD) versus a low risk group (ε3/3 homozygotes with no family history of AD) during letter fluency and object naming tasks relative to a low-level, resting baseline condition (responding to a grayscale square that randomly changed in intensity). These authors found that ε4 carriers displayed increased activation in the left parietal region during a letter fluency task, and reduced activation in the inferotemporal cortex during the object-naming task. Longitudinal follow-up of a smaller subset (N = 25) of these participants four years later with the same object naming task revealed a greater longitudinal decline in fMRI activation in the inferotemporal cortex of the ε4 carriers compared to ε3/3 homozygotes. Since object naming and letter fluency are generally affected after episodic memory symptoms appear in AD [64], it may be that an episodic memory task would be more helpful in assessing the primary area of early pathology in AD – the MTL [6].

Bookheimer et al. [65] compared brain activation differences between cognitively normal ε4 carriers and ε3/3 homozygotes (age range: 47–82 years) using a paired-associate task as a probe of episodic memory. In their task, subjects were to encode seven unrelated word pairs over six learning trials, in which each learning trial was followed by 30-second periods of rest. The encoding phase was followed by six recall trials in which subjects heard the first word of each pair and were asked to recall the second word silently. The major contrast used to examine group differences was encoding + recall relative to the resting baseline. Whole-brain analysis revealed greater activation in the left prefrontal cortex, bilateral orbitofrontal, superior temporal, and inferior and superior parietal regions in ε4 carriers relative to the ε3/3 homozygotes for the contrast of encoding + recall relative to rest. In follow-up ROI analyses, these authors reported that ε4 carriers displayed greater signal change in the left MTL as well. In a follow-up study, Burrgren et al. [66] reported no differences between ε4 carriers and ε3/3 homozygotes

during performance of a modified digit-span (forwards) working memory task relative to a baseline condition that was a single digit. They hypothesized that their results reflected a compensatory response in which ε4 carriers require additional cognitive effort to achieve comparable performance during episodic memory encoding tasks.

More recently, Bondi et al. [67] found that cognitivelyhealthy, older (mean age = 76) ε4 carriers displayed greater activation in the fusiform gyrus, parietal cortex and frontal gyrus compared to ε3/3 homozygotes using a paradigm in which subjects had to discriminate novel pictures from a single repeating picture. Follow-up ROI analysis revealed that ε3/3 homozygotes displayed greater activation in the left MTL compared to ε4 carriers, consistent with the findings of the present study. In contrast, the opposite pattern of results was found in the right MTL (i.e. ε4 carriers displayed greater activation in the right MTL). These authors also reported correlations between memory ability on a word-list learning task and right and left hippocampal activation during picture encoding (i.e. a positive correlation in ε3/3 homozygotes and a negative or zero correlation in carriers of the ε4 allele) that were similar to the correlations found in the present study. They suggested that their results were consistent with the compensatory response hypothesis described by Bookheimer et al. [65].

The exact reason for these contradictory findings is not knownp; however, there are several demographic and methodological differences between our study and the two previous fMRI studies that employed an episodic memory task. First, our subjects were on average 10 to 23 years younger than the participants in Bookheimer et al. [65] and Bondi et al [67], complicating comparisons between studies. Cabeza et al. [68] found that older individuals (mean age = 70 years) displayed reduced hippocampal activation during episodic retrieval, but greater activity in the prefrontal and parahippocampal cortices compared to young individuals (mean age = 23 years) [see also [69]]. Second, 60% of the subjects in Bookheimer et al. [65] had a family-history of AD, whereas 100% of our subjects had at least one biological parent with AD (Bondi et al. [67] did not report the percentage of subjects in his study with and without a family history of AD). Therefore, differences in these demographic variables might be responsible for the discrepant findings. Longitudinal studies similar to Smith et al. [63] that use episodic memory tasks and employ a 2 . 2 . 2 factorial design with family history of AD and APOE genotype as grouping variables are needed to help clarify these findings.

Third, it is possible that the divergent findings may have resulted from differences in the episodic memory task employed. In the present study, we employed a relatively straightforward novel/familiar discrimination paradigm as the probe of episodic encoding. In contrast, Bookheimer et al. [65] used a paired associate learning/recall task that was presumably more difficult than the paradigm used to define encoding in the present study [see [70]]. The paradigm used in the present study also differed from the encoding task used by Bondi et al. [67]. We presented familiar pictures in two separate trials before the fMRI scan. In contrast, first exposure to the repeating picture was during the fMRI task in the paradigm employed by Bondi et al. [67] and also by others e.g. [30], therefore some reduction in hippocampal signal during the presentation of the repeating novel stimulus may have occurred (see [50]).

Fourth, it is also possible that the compensatory response in ε4 carriers is more evident in elderly ε4 carriers rather than middle-aged ε4 carriers. Presumably, the negative effects of the APOE ε4 allele on hippocampal structure and function accelerate with increasing age. It is therefore possible that reduced hippocampal volume in elderly ε4 carriers [12-16,19,56,71] (but see [18]) might lead to the recruitment of

structures to compensate for accumulating neuropathology in the MTL. Smith et al. [62] suggested that increased activation in ε4 carriers might be caused by a disruption in upstream elements of a functional network, resulting in decreased input from regions that are affected early in AD such as the MTL.

Finally, an important methodological difference between our study and previous studies was the baseline condition used. In the present study, we contrasted novel relative to familiar pictures, whereas previous studies reporting increased activation in ε4 carriers used lower level baseline conditions. Since most fMRI designs employ a subtraction method (activation – baseline), the baseline task chosen has a major effect on brain activation patterns observed. Using rest as a baseline condition may augment unintended effects in the experimental task such as language or sensorimotor processes, and increase inter-subject variability in brain activation during the baseline condition since there is less control over the mental state of the subject (i.e. what is the subject thinking about during the resting condition?).

To address this issue, Stark and Squire [72] designed an elegant study to examine the effects of several different baseline conditions including resting fixation on MTL fMRI activation during presentation of novel and familiar pictures. These authors found that MTL activation to novel and familiar pictures was significantly greater when an active task was used as a baseline (in their case, an odd/ even number comparison task) than when passive rest was used as the baseline. In fact, several MTL regions were found to display increased activation during rest relative to familiar or novel pictures. In contrast, when the active baseline task was used, both novel and familiar pictures were associated with significant bilateral activity throughout much of the MTL. These authors suggested that using rest as the baseline condition may reduce, eliminate or even reverse the sign of activity during a cognitive task. At the very least, the lack of control over the mental state of subjects during the resting state makes it not ideal to serve as a baseline condition for comparison to cognitive tasks.

More recent evidence suggests that the hippocampus is coactive during the resting state with several cortical structures including precuneus and posterior cingulate cortex [73], and this resting state activation is disrupted in individuals with MCI and AD [74,75]. These new data make the previous findings of increased task-related activation relative to low-level baseline conditions in ε4 carriers more difficult to interpret, and argue against the use of resting baseline conditions in fMRI studies targeting these brain regions, especially in individuals with AD or at risk for AD.

Several positron emission tomography (PET) imaging studies have also reported reductions in resting state cerebral metabolic rate of glucose (CMRgl) in the MTL and cortical regions of AD patients and cognitively normal ε4 carriers between the ages of 20 and 65 years [76-82], suggesting different baseline neural activity in individuals at risk for AD. Reduced cerebral glucose utilization has also been shown to inhibit the induction of synaptic plasticity in the hippocampus of rats [83] and impair learning and memory on hippocampus-dependent tasks [84]. Prior research has demonstrated that CMRgl is coupled to regional cerebral blood flow (rCBF) [85,86], and both CMRgl [87] and rCBF [88,89] are coupled to the neural response. The current finding of reduced hippocampal BOLD signal during episodic encoding in ε3/4 heterozygotes is consistent with these studies, supporting the idea that reduced glucose metabolism would lead to reduced neuronal activation in the MTL during encoding. More research is needed to determine the relationship between reduced resting levels of CMRgl in ε4 carriers and task-related changes in the fMRI BOLD signal.

Reduced hippocampal activation in ε3/4 heterozygotes is consistent with several previous fMRI studies of memory encoding in patients with AD and MCI. For example, AD patients display reduced hippocampal activation compared to elderly controls during memory encoding [90,91], whereas no differences were found in the motor cortex during a sensorimotor task [90]. Machulda et al. [90] also reported similar findings in MCI patients [see also [92]]. Johnson et al. [50] found that elderly normal subjects displayed a hippocampal adaptation response (i.e. reduction in signal intensity) to repeating unfamiliar faces that was not displayed by age-matched patients with MCI. Taken together, these prior results indicate that MTL activation is reduced in AD and MCI patients with objective memory impairment relative to elderly, cognitively normal controls.

In a recent study, Dickerson et al. [93] examined differences in the extent of brain activation (i.e. number of contiguous as well as non-contiguous voxels), but not the magnitude of activation, during episodic encoding in AD patients and elderly individuals with and without subjective memory complaints who did not meet the clinical criterion for MCI [94]. These authors manually traced bilateral ROIs of the hippocampus and entorhinal cortex from each participant's structural MRI. They found that individuals with memory complaints displayed increased extent of activation in each of the four ROIs relative to age-matched subjects with no memory complaints. AD patients were found to display significantly less extensive activation relative to both groups. Furthermore, APOE ε4 carriers were found to display a greater extent of activation relative to non-carriers when collapsed across the memory complaints factor.

Dickerson et al. [93] suggested that increased extent of MTL activation early in the course of prodromal AD was followed by a subsequent decrease in the extent of activation as the disease progresses. An important caveat to these findings is that the individuals with memory complaints had significantly greater education and total word recall on a word-list learning task relative to individuals without memory complaints. Therefore, increased extent of activation may have been related to the paradoxically better encoding ability in individuals with memory complaints. This interpretation is supported by the finding of the present study that total word recall on the RAVLT was associated with increased magnitude of activation during episodic encoding, at least in the ε3/3 homozygotes. Previous studies have also reported similar findings [60,95,96], suggesting that individuals with better episodic memory ability display greater fMRI activation in the MTL during episodic encoding tasks.

Reduced neural function in the MTL of asymptomatic ε4 carriers may also lead to a greater age-related decline in episodic memory over time. Several studies have reported that older ε4 carriers display significantly greater longitudinal age-related decline in episodic memory functions than non-carriers [9-11,97,98]. For example, Caselli et al. [97] reported that cognitively normal ε4 carriers (mean age = 60 years) displayed significantly greater longitudinal decline during a three-year follow-up period for total word recall on the RAVLT and delayed recall of complex figures. Our findings that hippocampal activation during a novel-picture encoding task is reduced in ε3/4 heterozygotes, and that memory encoding ability is positively associated with anterior MTL activation in ε3/3 homozygotes but not ε3/4 heterozygotes, are consistent with previous findings that MTL-dependent memory processes decline at a greater rate in individuals who are ε4 carriers and have a family history of AD. These results leave open the possibility that ε4 carriers recruit other brain regions and/or rely on other compensatory psychological processes (e.g. verbal rehearsal of visual information) during encoding to compensate for early

pathological changes in MTL structure and function [65,67].

Studies in transgenic mice expressing a human form of the APOE ε4 allele also support the negative effects of the ε4 allele on hippocampal function. For example, the presence of the APOE ε4 allele increases the production of βamyloid (the main constituent of the senile plaques in AD) in cultured hippocampal neurons [99], reduces synaptic plasticity in the hippocampus [100], promotes βamyloid induced blockade of plasticity in the hippocampus [101] and impairs hippocampus-dependent spatial memory [102,103]. Our results are consistent with these findings as well.

This study has several limitations. We did not include a lowlevel baseline condition (for the reasons discussed above), limiting our ability to compare and contrast our results directly to previous fMRI studies of APOE genotype. Furthermore, the findings of fMRI activation differences associated with APOE genotype were restricted to ε3/3 homozygotes and ε3/4 heterozygotes with a parental history of AD. Therefore, our results only generalize to individuals with these APOE genotypes and a family history of AD. More studies are needed to determine the effects of other APOE genotypes (e.g. ε4/4, ε2/3) and family history of AD on brain activation during memory encoding. Third, we also did not include a post-scan recognition memory test to determine if the novel pictures were encoded into memory. While conclusions regarding APOE genotype differences in encoding related processes cannot be made directly from this study, they can be inferred on the basis that novel information is more likely to be encoded than familiar information (see also [31]).

Fourth, several of the subjects in this study had elevated total blood cholesterol and/or high blood pressure. Importantly, there were no group differences in the percentage of subjects with these conditions, and these percentages were also no greater than observed prevalence rates in the general US population. Fifth, several subjects in each group were current users of medications that influence brain function and may affect the hemodynamic BOLD response. More studies are needed to determine the effects of these drugs and/or medical conditions on the fMRI signal. Finally, the subjects in this study were predominantly Caucasian, highly educated and female. Additional studies are needed to determine whether our findings can be confirmed in subjects with other demographic characteristics. Despite these limitations, the results of the present study provide converging evidence for the idea that the MTL displays functional decline associated with the APOE ε4 allele in individuals with a family history of AD.

If compromised MTL function continues to be observed in healthy ε4 carriers, this group of subjects may represent a good study population for novel treatments designed to delay the onset of or to prevent AD. More studies are needed to clarify inconsistent findings and to determine the reliability, validity and clinical utility of hippocampal activation paradigms for the early detection of AD. Although the results of the present study indicate cross-sectional differences in MTL activation based on APOE genotype, future studies employing longitudinal designs will be required to determine whether or not differences in MTL activation in individuals at genetic risk for AD can be used to improve the detection of incipient AD.

Conclusion

This study found that APOE ε3/4 heterozygotes with a family-history of AD displayed reduced activation compared to ε3/3 homozygotes in the MTL during a novel picture-encoding task. Importantly, these changes occurred in the absence of cognitive differences between the groups. We also found that greater encoding ability on a neuropsychological measure of learning (i.e. RAVLT) was positively associated with fMRI activation in the left anterior MTL in the ε3/3 homozygotes but not in the ε3/4

heterozygotes. Together with previous studies reporting reduced glucose metabolism and AD-related neuropathology, this study provides convergent validity for the idea that the MTL exhibits functional decline associated with the APOE ε4 allele.

Competing interests

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

Authors' contributions

MAT and TWS carried out the statistical analysis, drafted the manuscript and assisted in the acquisition of data. MLR, BMT and SA assisted in data acquisition and drafting of the manuscript. MAS and BPH assisted in data acquisition, interpreting the results and drafting the manuscript. SCJ drafted the manuscript, conceived of the study concept and design, assisted in the statistical analysis and interpretation of the results. All authors read and approved the final manuscript.

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SAFETY AND EFFICACY OF A GENERIC FIXED-DOSE COMBINATION OF STAVUDINE, LAMIVUDINE AND NEVIRAPINE ANTIRETROVIRAL THERAPY BETWEEN HIV-INFECTED PATIENTS WITH BASELINE CD4 <50 VERSUS CD4 ≥ 50 CELLS/MM^3

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Antiretroviral therapy (ART) with a generic fixed-dose combination (FDC) of stavudine (d4T)/lamivudine (3TC)/nevirapine (NVP) is widely used in developing countries. The clinical data of this FDC among very advanced HIV-infected patients is limited.

Methods: A retrospective cohort study was conducted among ART-naive HIV-infected patients who were initiated a generic FDC of d4T/3TC/NVP between May 2004 and October 2005. Patients were categorized into 2 groups according to the baseline CD4 (group A: <50 cell/mm^3 and group B: ≥ 50 cell/mm^3).

There were 204 patients with a mean ± SD age of 37.1 ± 8.9 years, 120 (58.8%) in group A and 84 (41.2%) in group B. Median (IQR) CD4 cell count was 6 (16–29) cells/mm^3 in group A and 139 (92–198) cells/mm^3 in group B. Intention-to-treat analysis at 48 weeks, 71.7% (86/120) of group A and 75.0% (63/84) of group B achieved plasma HIV RNA <50 copies/ml (P = 0.633). On-treatment analysis, 90.5% (87/96) in group A and 96.9% (63/65) in group B achieved plasma HIV RNA <50 copies/ml (P = 0.206). At 12, 24, 36 and 48 weeks of ART, mean CD4 were 98, 142, 176 and 201 cells/mm^3 in group A and 247, 301, 336 and 367 cells/mm^3 in group B, respectively. There were no differences of probabilities to achieve HIV RNA <50 copies/ml (P = 0.947) and CD4 increment at 48 weeks between the two groups (P = 0.870). Seven (9.6%) patients in group A and 4 (8.5%) patients in group B developed skin reactions grade II or III (P = 1.000). ALT at 12 weeks was not different from that at baseline in both groups (P > 0.05).

Initiation of FDC of d4T/3TC/NVP in HIV-infected patients with CD4 <50 and ≥ 50 cells/mm^3 has no different outcomes in terms of safety and efficacy. FDC of d4T/3TC/NVP can be effectively used in advance HIV-infected patients with CD4 <50 cells/mm^3.

Background

Current antiretroviral treatment guidelines for HIV infection in adults and adolescents in the resource-limited settings recommend using two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI) as the first-line antiretroviral regimen [1,2]. Regimens based on these combinations are efficacious, are generally less expensive, have generic formulations and are available as generic fixed-dose combinations (FDC). To date, two NNRTIs are currently available for clinical use in the treatment of HIV disease. Either nevirapine (NVP) or efavirenz (EFV) has shown antiretroviral efficacy [3-5]. A recent large investigation has demonstrated that both drugs have similar antiviral efficacy among antiretroviral naive HIV-infected patients [5].

Although EFV-based ART is an NNRTI-based antiretroviral therapy (ART) of choice according to the recommendation of recent antiretroviral treatment guidelines [1,2], NVP-based HAART has been extensively used in the developing countries due to its accessibility. Since 2002, the Thai Government Pharmaceutical Organization (GPO) has produced a FDC of 30 or 40 mg stavudine (d4T), 150 mg lamivudine (3TC) and 200 mg nevirapine (NVP). This combination formula makes dosing simple

(one tablet twice daily) and facilitates drug supply procedure for the national ART program. The previous study of bio-equivalence showed that NVP concentrations were within international and manufacturer's standard [6]. In addition, World Health Organization (WHO) guideline recommends a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and one NNRTI as first-line regimen in resource-poor settings due to available evidences, clinical experience and programmatic feasibility for the wider introduction of ART [7]. The Medecins Sans Frontieres (MSF) cohort result recently demonstrated the efficacy and safety of generic FDC in preventing AIDS-related death in resource-limited settings [8].

There are some potential limitations of NVP-based ART including adverse drug reactions and low genetic barrier. Skin rash is the most frequently observed adverse event from NVP and manifests as a diffuse maculopapular rash or erythematous rash with or without constitutional symptoms. The risk of rash at any severity is greatest in the first six weeks [9]. However, the severe rashes have been reported [10-13].

To date, the data regarding safety and efficacy of the d4T/ 3TC/NVP FDC among advanced HIV-infected patients with very low CD4 is still limited. Patients in resource-limited settings usually present late with very low CD4 cell counts. We therefore conducted this retrospective cohort study to compare immunological and virological out comes and adverse events of a generic FDC of d4T/3TC/ NVP between HIV-infected patients who had baseline CD4 cell counts <50 cells/mm^3 and those who had CD4 cell counts ≥50 cells/mm^3.

Methods

A retrospective cohort study was conducted among ART-naive HIV-infected patients who were initiated a generic FDC of d4T/3TC/NVP between May 2004 and October 2005 in Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Nonthaburi, Thailand. The patients' identification numbers were identified from annual database of the institute. The data were extracted from the medical records. Inclusion criteria were as follows: (1) HIV-infected individuals ≥ 15 years old, (2) naive to ART prior to FDC of d4T/3TC/NVP, (3) were initiated with a generic FDC of d4T/3TC/NVP, (4) used separate tablet of NVP 200-mg once-daily lead-in dose during the first 2 weeks, prior to escalation to 200 mg twice daily, (5) followed up at least two clinic visit. Exclusion criteria were as follows: (1) baseline serum creatinine level > 2.0 mg/ml, (2) baseline liver aminotransferase >3 times of upper normal limit, (3) currently active major opportunistic infections (OIs), and (4) receiving medications that have drug-drug interactions with NVP, including rifampicin and fluconazole.

All eligible patients were categorized into two groups according to their baseline CD4 cell counts: group A (CD4 cell count <50 cells/mm^3) and group B (CD4 cell counts ≥ 50 cells/mm^3). Factors including demographics, previous OIs, CD4 cell counts, plasma HIV RNA were studied and compared between the two groups. Patients were followed up for 48 weeks after initiation of a generic FDC of d4T/3TC/NVP. The parameters including CD4 cell counts, plasma HIV RNA and ALT were assessed at baseline, 12, 24, 36 and 48 weeks of ART. The primary outcome of interest was the proportion of patients who achieved plasma HIV RNA <50 copies/ml after 48 weeks of ART. The secondary outcomes were as follows: 1) the probability to achieve plasma HIV RNA <50 copies/ml, 2) the increment of the number of CD4 cell counts at 48 weeks of ART from baseline value and 3) the incidences of NVP-associated adverse reactions including skin rashes and hepatotoxicity that lead to drug discontinuation.

The severity of skin rashes was determined as Level I: erythema; Level II: diffuse maculopapular rash or urticaria;

Level III: rash with constitutional symptoms, angioedema, serum sickness-like reactions, Stevens Johnson syndrome; Level IV: toxic epidermal necrolysis. The virological failure was defined as either a rebound plasma HIV RNA of >1,000 copies/ml after having previously undetectable value or lack of achievement to <50 copies/ ml at 24 weeks of ART.

Mean (± SD), median (interquartile range, IQR) and frequencies (%) were used to describe patients' characteristics in both groups. *Chi*-square test and Mann-Whitney U test were used to compare categorical variables and continuous variables between the two groups, respectively. The proportion of patients with plasma HIV RNA <50 copies/ml after 48 weeks of ART were analyzed as intention-to-treat and on-treatment analysis. Missing data on plasma HIV RNA levels were taken to be greater than 50 copies/mL. The increment of CD4 cell counts between the two groups were compared by Mann-Whitney U test. The Kaplan-Meier test was used to estimate the probability of undetectable plasma HIV RNA at 12, 24, 36 and 48 weeks after ART and the median time to undetectable plasma HIV RNA. The patients were censored when they had virological failure or discontinued the FDC due to any causes. The patients who had been on drug holidays longer than 4 weeks were considered as lost to follow-up and censored at the date of first lost to follow-up visit. The log-rank test was used to compare the median time to undetectable plasma HIV RNA between the two groups. The multivariate Cox proportional hazard model was used to determine the chance of undetectable plasma HIV RNA after receiving treatment by adjusting for confounding factors, i.e. age, gender, previous OIs, baseline hemoglobin, CD4 cell counts (<50 versus ≥ 50 cells/mm^3) and plasma HIV RNA at baseline. Statistical calculations were performed using SPSS program version 11.5 (SPSS Inc., Chicago, Illinois, U.S.A). A two-sided *P* value of less than 0.05 was considered statistically significant. The study was approved from the institute review board.

Results

A total of 204 patients met entry criteria; mean (± SD) age was 37.1 ± 8.9 years and 60.3% were male. There were 120 (58.8%) patients in group A and 84 (41.2%) patients in group B. Table 1 shows baseline characteristics between the two groups. Median (IQR CD4 cell count was 6 (16– 29) cells/mm^3 in group A and 139 (92–198) cells/mm^3 in group B. Group A had more previous opportunistic infections, higher baseline HIV RNA, ALP and ALT than group B (P < 0.05). Any causes of discontinuation of ART are shown in Table 2. There were no differences of the causes of discontinuation between the two groups. Of 204 patients, 162 patients had ALT values at 12 weeks after ART. Two of 95 (2.1%) patients in group A and 1 of 64 (1.6%) patients in group B had ALT elevation at grade 3– 4 (P = 1.000).

The results of the primary outcome are shown in Table 3. There were no differences of proportion of patients who achieved plasma HIV RNA <50 copies/ml between the two groups, either in intention-to-treat analysis or on-treatment analysis. Cox regression of possible risk factors for achieving undetectable plasma HIV RNA is shown in Table 4. The results of Kaplan-Meier analysis to estimate the probability of undetectable plasma HIV RNA after receiving treatment are shown in Figure 1. We found that such probabilities at 12-, 24- and 36-month were 65.1%, 92.4% and 92.4% for group A. The corresponding values were 67.6%, 89.7% and 89.7% for group B. There was no difference between the two groups (log rank test, P = 0.947). The Cox proportional hazard model including factors of age, gender, body weight, previous OIs, baseline hemoglobin, baseline CD4 cell counts and baseline plasma HIV RNA showed that patients in group A had similar chance of undetectable plasma HIV RNA

with the patients in group B (HR = 0.986, 95%CI = 0.669–1.391, P = 0.934). The other factors were not associated with undetectable plasma HIV RNA after 48 weeks of ART (P > 0.05).

Group A patients had a median CD4 cell count of 85, 125, 158 and 198 cells/mm3 and group B patients had a median CD4 of 240, 280, 305 and 331 cells/mm3 at 12, 24, 36 and 48 weeks, respectively (Figure 2). The increment of median (IQR) CD4 cell counts at 48 weeks from baseline values were not different between the two groups [179 (121–226) cells/mm3 vs. 168 (99–273) cells/mm3, P = 0.870]. Eleven (9.2%) patients in group A and 12 (14.3%) patients in group B developed NVP-associated skin reactions grade II and III in which lead to the discontinuation of generic FDC of d4T/3TC/NVP (P = 1.000). Mean ± SD ALT when these 23 patients developed skin reaction was 31.5 ± 21.1 U/l. No patients in the present study developed skin reactions grade IV. By repeated measurement analysis, there were no differences of ALT at 12 weeks from baseline value in both groups (P > 0.05). No patients developed clinical hepatitis. Three (2.5%) patients in group A and 5 (6.0%) patients in group B developed stavudine-associated peripheral neuropathy (P = 0.278). Stavudine-associated symptomatic lactic acidosis was observed in 2 patients during the 48-week study period. Four patients in group A and one patient in group B died during the study period. The causes of death of these 5 patients were as follows: disseminated histoplasmosis 1, E. coli sepsis 1, MAC infection 1 and wasting syndromes 2.

Discussion

The results from the present study demonstrate that HIV-infected patients who had baseline CD4 cell counts <50 cells/mm^3 had similar virological and immunological responses when compared to those who had baseline CD4 cell counts ≥ 50 cells/mm^3. This finding can support the use of this generic FDC of d4T/3TC/NVP in very advanced HIV-infected patients in the resource-limited settings. According to the guideline for management of HIV-infected patients in Thailand, ART is recommended for all patients with history of AIDS-defining illness or asymptomatic patients with CD4 cells count less than 200 cell/mm^3.

Table 1. Baseline characteristics of 204 patients

Characteristics	Group A (n = 120)	Group B (n = 84)	P value
Age, years, mean ± SD	37.6 ± 8.0	36.9 ± 10.1	0.289
Male gender	70 (58.3%)	53 (63.1%)	0.561
Body weight, Kgs, mean ± SD	54.3 ± 10.3	56.1 ± 13.8	0.766
Previous major OIs	41 (34.2%)	11 (13.1%)	0.001
Baseline hemoglobin, mg/dl, median (IQR)	10.7 (8.4–12.0)	11.5 (9.5–13.3)	0.035
Baseline CD4, cell/mm3, median(IQR)	6 (16–29)	139 (92–198)	<0.001
Baseline CD4%, median (IQR)	2 (1–2)	8 (0–13)	<0.001
Baseline plasma HIV RNA, copies/ml, median (IQR)	357,000 (187,000–727,750)	231,000 (69,750–645,250)	0.027
Baseline ALP, U/I, median (IQR)	91.0 (71.0–128.0)	74.5 (58.0–94.2)	<0.001
Baseline ALT, U/I, median (IQR)	32.0 (18.0–50.0)	21.5 (16.0–33.5)	0.003
Baseline total bilirubin, mg/dL, median (IQR)	0.5 (0.4–0.7)	0.5 (0.4–0.7)	0.532

Therefore, almost all patients in group B have baseline CD4 cell counts between 50 cells/mm^3 and 200 cells/mm^3. As expected, group A patients have a higher proportion of previous opportunistic infections and a higher level of plasma HIV RNA.

The overall proportion of patients who achieved plasma HIV RNA <50 copies/ml was 73% (149 of 204) after 48 weeks of ART in an ITT analysis. Despite the fact that

group A patients were severely immunocompromised (median baseline CD4 cell count of 6 cells/mm^3), we found that 71% of patients achieved undetectable plasma HIV RNA after 48 weeks of ART. This number is comparable to the virological response in group B and similar to other studies that conducted in our country and in developed countries [5,14-16]. Moreover, this outcome is confirmed by the analysis of probability of achieving plasma HIV RNA <50 copies/ml as shown in Figure 1. Although the patient in group A had a significantly higher baseline plasma HIV RNA than that in group B, the rates of achieving undetectable plasma HIV RNA are not different between group A and group B, by either univariate or multivariate analysis.

The well-established predictors of long-term virological success include potency of ART regimen, adherence to treatment, low baseline viremia, higher baseline CD4 cell counts and rapid reduction of viremia in response to treatment [17,18]. In the present study, the difference baseline CD4 cell counts and baseline plasma HIV-RNA did not affect virological responses after 48 weeks of treatment. This may be explained by the fact that this study did not include patients with CD4 cell count of greater than 200 cells/mm^3, as in previous studies. HIV-infected patients in developing countries usually present late with low CD4 cell counts as previously mentioned. A recent study in a developing country also demonstrated that there was a high rate of virological and immunological success after six months of HAART, irrespective of the pre-HAART viral load and CD4 cell count [19].

Overall, CD4 cell counts rise with immune recovery from receiving ART. The increment of CD4 cell counts after 48 weeks of ART is not blunted with very low baseline CD4 cell counts as shown in Figure 2. Even in subgroup of patient with baseline CD4 cell counts less than 10 cells/ mm^3, they can achieve effective immune recovery by given sufficient time after initiation of ART. Median (IQR) CD4 cell counts increase from 5 (3–7) cells/mm^3 to 151 (92– 231) cells/mm^3 in this subgroup (data not shown). This response would be continued for many years into effective antiviral effect of ART.

Regarding discontinuation of ART, NVP-associated skin rashes is an important reason for discontinuation. In the present of NVP 200-mg once-daily lead-in for 2 weeks, NVP may cause a mild skin rash in 15 to 20% of patients; 5 to 10% of which discontinue treatment [5,20,21]. After48 weeks of ART, 11.3% of patients in the present study developed skin rashes in which lead to permanent discon tinuation of NVP.

Table 2. Causes of ART discontinuation between the 2 groups

Causes of discontinuation	Group A (n = 120)	Group B (n = 84)	*P* value
NVP-associated skin rashes grade II, III and IV	11 (9.2%)	12 (14.3%)	0.269
Virological failure	9 (7.5%)	2 (2.4%)	0.129
Lost to follow-up	7 (5.8%)	5 (6.0%)	1.000
Died	4 (3.3%)	1 (1.2%)	0.651
Referred to other hospitals	1 (0.8%)	0*	1.000
d4T-associated lactic acidosis	1 (0.8%)	1 (1.2%)	1.000

* Substitute 0 as 1 to calculate *P* value

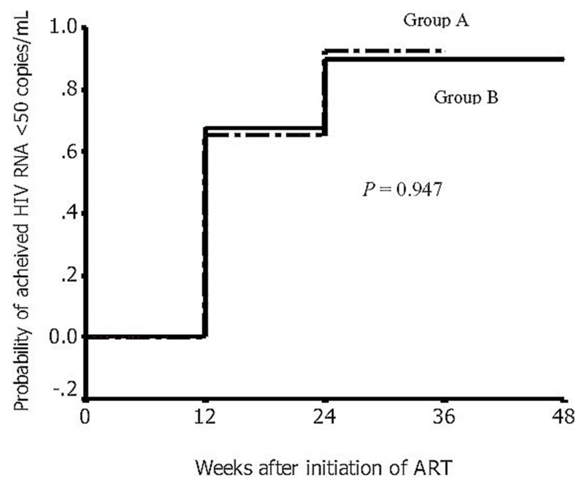

Figure 1. Probability of undetectable plasma HIV RNA between the 2 groups.

This rate is similar to that in the previ ous study in Thais [14,22]. Of note, Steven-Johnson's syndrome and toxic epidermal necrolysis were not observed in this cohort in whom almost all of patients (91%) in the study had baseline CD4 cell counts less than 200 cells/mm3. Furthermore, no factors (i.e., gender and CD4 cell counts) were associated with skin rashes in the present study according to the results of logistic regression analysis (data not shown).

Table 3. Virological response between the two treatment groups at 48 weeks

	Percentage of patients who achieved HIV RNA< 50 copies/ml		Relative Risk, 95% confidence interval	*P* value
	Group A	Group B		
ITT*	71.7% (86/120)	75.0% (63/84)	0.843, 0.447–1.589	0.633
OT**	90.6% (87/96)	96.9% (63/65)	0.303, 0.063–1.453	0.202

* Intention-to-treat analysis ** On-treatment analysis

Table 4. Cox regression of possible risk factors for achieving undetectable plasma HIV RNA at 48 weeks

Risk factors	HR	95% CI	*P* value
Age	1.000	0.980–1.020	0.993
Gender	0.948	0.661–1.513	0.774
Weight	0.998	0.983–1.013	0.778
Previous OIs	0.979	0.660–1.451	0.916
Hemoglobin	1.000	1.000–1.000	0.533
Baseline CD4 cell counts<50 cells/ mm3	1.000	0.998–1.002	0.880
Baseline log plasma HIV-RNA	0.764	0.549–1.064	0.111

HR = Hazard ratio, 95% CI = 95% Confidence interval

These findings suggest that there is no clinical factor to predict the occurrence of rash from NVP in patients with very low CD4 cell counts. However, this should be interpreted with caution due to the limitation of sample size. It would be beneficial if there are any factors that can predict this adverse event. Further study to determine immunologic and genetic factors that associated with rash is encouraged.

Although there are limited data regarding the impact on hepatotoxicity, we decided to exclude the patients who concurrently received rifampicin and fluconazole from the study. These drugs may potentially increase incidence of hepatotoxicity [23-25]. The previous studies demonstrated that woman with higher CD4 cell counts appear to be at a highest risk. A 12-fold higher incidence of symptomatic events was seen in woman with CD4 cell counts of >250 cells/mm^3 at the time of nevirapine initiation when compared with woman with CD4 cell counts of ≤ 250 cells/mm^3 (11.0% vs 0.9%). An increased risk was also seen in men with baseline CD4 cell counts >400 cells/ mm^3 when compare with baseline CD4 cell counts ≤ 400 cells/mm^3 (6.3% vs 1.2%) [26-29]. The present study show that no patients developed clinical hepatitis after 48 weeks of follow-up. In addition, neither group A patients nor group B patients had significant increment of liver enzymes after 12 weeks of ART when compare to baseline values. Overall, the frequencies of clinical hepatitis and hepatic laboratory abnormalities were low in both groups. In the present cohort, stavudine-associated symptomatic lactic acidosis was observed in 2 patients after 48 weeks of treatment. Although this number is low, this well-established adverse event should be closely monitored in the further long-termed treatment.

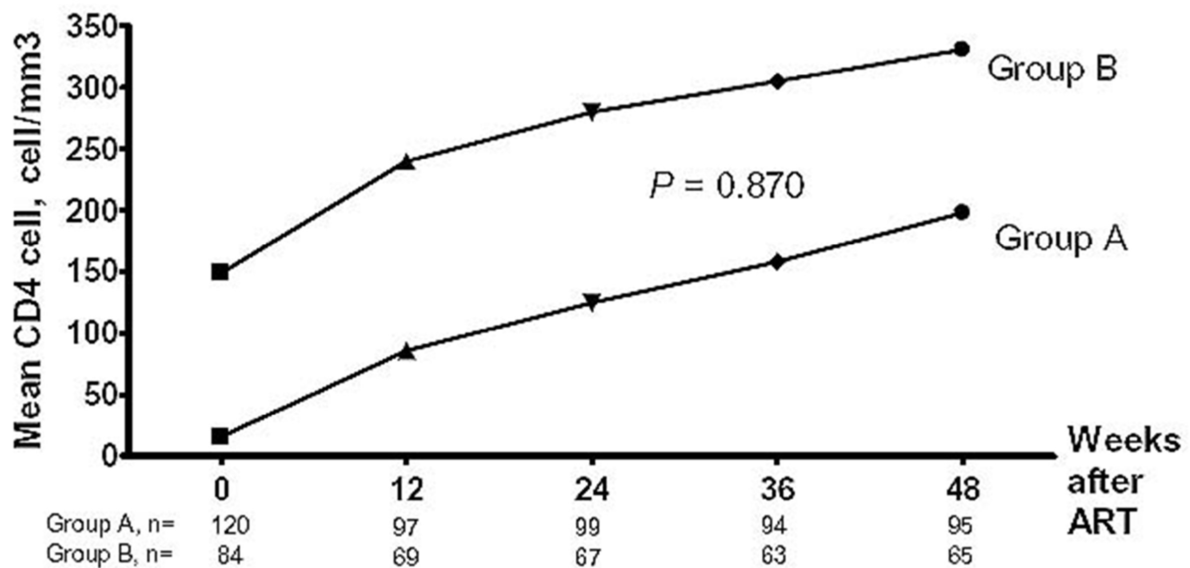

Figure 2. Immunological outcomes between the 2 groups at 48 weeks of ART.

Currently, stavudine is not a first-line antiretroviral drug recommended in the recent guideline of developed country due to its significant toxicities [7]. Additionally, eight patients needed to discontinue stavudine due to peripheral neuropathy. Until more options are accessible, stavudine is still a part of a simplified strategy for scaling-up ART in resource-poor settings according to previously mentioned benefits.

The study has demonstrated the satisfactory clinical outcomes, the extent of

immunological restoration and virological responses of a generic FDC of d4T/3TC/NVP in very advanced HIV-infected patients. These results provide the evidence of benefit from NVP-based ART in advanced HIV-infected patients. Thus, this may support the physicians to prescribe NVP-based ART regimen for these patients.

The present study has some limitations. The study design is a retrospective study, which is not the best study design to evaluate the efficacy of antiretroviral regimen. However, this study design is a comparative study that evaluated the efficacy NVP-based ART between the patients who had extremely low CD4 cell counts and those who had moderate level of CD4 cell counts. The results of the present study may provide useful clinical data for caring advanced HIV-infected patients in developing countries. In addition, some clinical data may be underestimated and some possible risk factors may not be included. Our study was based on a tertiary care center for HIV-infected patients. These study populations were cared by infectious diseases specialists and HIV-experienced medical team. Thus, the similar results might not be achieved in the general or community hospital in resource-limited setting. Liver enzymes were not performed during the first few weeks of ART. However, no patients developed clinical hepatitis during this period. Baseline hepatitis B and hepatitis C serology were not routinely performed prior to ART initiation. We did not have reference group of patients with CD4 cell counts greater than 200 cells/mm^3. It would be more interesting if we can compare clinical outcomes between these groups. Finally, the sample size may be not large enough to detect small difference of efficacy and low incidence of adverse events, particularly hepatitis.

In conclusion, initiation of a FDC of d4T/3TC/NVP in HIV-infected patients with baseline CD4 cell count of <50 and ≥ 50 cells/mm^3 has no different outcomes in terms of safety and 48-week virological and immunological response. Generic FDC of d4T/3TC/NVP can be effectively used in advance HIV-infected patients with CD4 <50 cells/ mm^3.

Abbreviations

HAART: Highly active anti-retroviral therapy, HIV: Human immunodeficiency virus, NRTIs: Nucleoside reverse transcriptase inhibitors, NVP: NNRTs: Non-nucleoside reverse transcriptase inhibitors, FDC: Fixed-dose combinations, Nevirapine, EFV: Efavirenz, d4T: Stavudine, 3TC: Lamivudine, ART: Antiretroviral therapy, OIs: Opportunistic infections, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Competing interests

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

Authors' contributions

WM participated in the design of the study and statistical analysis. SC participated in the design of the study. SL participated in the design of the study. SS participated in the design of the study and statistical analysis.

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PERCEPTIONS OF VAGINAL MICROBICIDES AS AN HIV PREVENTION METHOD AMONG HEALTH CARE PROVIDERS IN KWAZULU-NATAL, SOUTH AFRICA

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The promise of microbicides as an HIV prevention method will not be realized if not supported by health care providers. They are the primary source of sexual health information for potential users, in both the public and private health sectors. Therefore, the aim of this study was to determine perceptions of vaginal microbicides as a potential HIV prevention method among health care providers in Durban and Hlabisa, South Africa, using a combination of quantitative and qualitative methods.
During 2004, semi structured interviews with 149 health care providers were conducted. Fifty seven percent of hospital managers, 40% of pharmacists and 35% of nurses possessed some basic knowledge of microbicides, such as the product being used intra-vaginally before sex to prevent HIV infection. The majority of them were positive about microbicides and were willing to counsel users regarding potential use. Providers from both public and private sectors felt that an effective microbicide should be available to all people, regardless of HIV status. Providers felt that the product should be accessed over-the-counter in pharmacies and in retail stores. They also felt a need for potential microbicides to be available free of charge, and packaged with clear instructions. The media was seen by health care providers as being an effective strategy for promoting microbicides.
Overall, health care providers were very positive about the possible introduction of an effective microbicide for HIV prevention. The findings generated by this study illustrated the need for training health care providers prior to making the product accessible, as well as the importance of addressing the potential barriers to use of the product by women. These are important concerns in the health care community, and this study also served to educate them for the day when research becomes reality.

Background

Evidence from studies of the female condom ([1-5]), emergency contraception [6], and medical abortion ([7,8]) reminds us of the potent influence that health care providers' (HCPs') beliefs and attitudes can have on the promotion of these technologies to potential users (PUs). In the field of HIV prevention, emerging technologies like microbicides have the potential to impact public health significantly, and the role that HCPs play as their patients' primary source of HIV and STI information will be crucial in successfully dispensing, educating and providing access to microbicides, once they become available [9].

Mantell and colleagues (2005) have discussed the intro-duction of the female condom in the early nineties, draw-ing the comparison with microbicides as a novel, women – initiated HIV prevention method [4,10]. The female condom has not had the

impact on reducing HIV trans-mission that researchers had hoped for, and this is due in large part to the lack of acceptability research among HCPs prior to introduction. Most research was conducted after the female condom had been introduced, and HCPs were often unprepared to counsel and educate PUs into making informed choices regarding its use [10]. With the female condom, a lack of awareness among HCPs regard-ing design features, cost as well as unfamiliarity with vari-ous physical characteristics of the product, also contributed to low acceptability among PUs [10].

Drawing on the lessons learnt from the female condom, researchers in the field of microbicides are now keenly aware of the importance of acceptability studies among HCPs prior to product introduction

Sub-Saharan Africa is bearing the brunt of the HIV pan-demic, with women accounting for a large part of new infections. HCPs beliefs and attitudes in sub-Saharan Africa, as well as the role they play as educators, have been found to significantly influence PUs acceptance of a prod-uct [2-4]. Bearing this in mind, as well as the fact that new HIV infections occur mostly among women in this region, it becomes critical that researchers investigate HCPs level of awareness and opinions regarding the promotion of vaginal microbicides as an HIV prevention method.

HCPs' also play a key role in determining the best chan-nels for access and distribution of novel HIV prevention and reproductive health methods[6,8,10,14]. In countries with high HIV and AIDS prevalence, public sector work-load and resources are severely strained and may limit HCPs' ability to promote and market microbicides to PUs' [14]. Moreover, there has been a dearth of research on the impact of the health care delivery systems on the adoption of new disease prevention technologies and the need for adaptations in service provision. As such, it is not known how HCPs will cope with the potential introduction of a microbicide. Therefore, one of the objectives of the present study was to investigate HCPs opinions regarding channels for delivery, access and distribution.

This study conducted by the Medical Research Council of South Africas' HIV Prevention Research Unit (HPRU), rep-resents the first comprehensive attempt to understand the views of HCPs with regard to promoting potential micro-bicides. The participants were not given information on microbicides prior to data collection by the interviewers. However, the study was conducted in areas where exten-sive education was provided to the community at large, including HCPs

Methods

Ethical approval

Ethical approval was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC). Approval was obtained from the KwaZulu-Natal Provincial Department of Health to approach public hos-pital staff, whilst private sector health care providers were approached directly by project staff.

Study population and setting

The study population consisted of 149 HCPs recruited from 53 clinics and hospitals. The majority of these were facilities that serviced the public sector (49/53), whilst the remainder were private hospitals (4/53). Their locations were in the city of Durban and the rural district of Hlabisa in KwaZulu-Natal Province, South Africa. All private hos-pitals were situated in Durban. Since the majority of the South African population access services through the pub-lic health service due to economic reasons, the researchers purposively sampled more HCPs from this sector. Clinics were randomly selected by health districts using the pro-vincial Department of Health's list of health care centres.

The 149 HCPs recruited consisted of 14 hospital managers (HMs), 10 pharmacists and 125 nurses. Participants were purposively sampled, and more nurses were

recruited since they form the backbone of public sector health serv-ices. Physicians were not included since they do not inter-act with PUs to the extent that nurses do. Traditional healers were also not included in the sampling as the study was focused on HCPs from the formal health sector. Pharmacists were included since they are ideally posi-tioned to increase people's access to microbicides, in terms of product placement and dispensing. Numerous clinics are often serviced by a single pharmacist, thereby accounting for the lower number of pharmacists sampled. Hospital Managers were recruited so as to obtain views on access and distribution, as well as capacity building needs with regard to a potential large-scale microbicide roll-out. The majority of HCPs were recruited from Durban, since Hlabisa has a limited public health service sector with only 20/125 nurses and 1/10 pharmacists being recruited from the latter area. Refer to Figure 1 that shows the population and setting breakdown.

Data collection and procedures

Data collection for the study took place between February and November 2004. A semi-structured key informant interview (SSI) with each HCP was conducted. The SSIs consisted of both closed and open-ended questions and were used to obtain individual perspectives from the HCPs professional position.

Focus Group Discussions (FGDs) were also held with the Chief Professional Nurses (CPNs) from the local health authority. All CPNs were sampled to represent clinic areas in Durban and there were 5 FGDs with between 7 and 12 members per FGD. 90% of the participants were women, as there are few men in the nursing services in the public sector. The FGDs were aimed at understanding the group dynamics that might impact on nurses' attitudes towards potential microbicides.

At each facility, researchers met with managers and staff to discuss the project and recruitment strategy. A team mem-ber described the study purpose, procedures, audio-recording, confidentiality, and obtained informed con-sent. Interview appointments were thereafter scheduled with some HCPs, whilst others were interviewed at the time of study recruitment.

Semi-structured interviews

The SSI explored four core domains: Section A dealt with *participants' socio-demographic details* (gender, area and type of practice, race, and religious affiliation).

Section B focused on *descriptions and opinions about micro-bicides*. This section questioned HCPs on their awareness of microbicides, source, and content of information; when information was acquired; opinion on its use for HIV prevention; target groups and age restrictions for pro-motion; disease prevention effectiveness relative to con-doms; and intentions to recommend to others.

Section C dealt with *barriers to and facilitators of the intro-duction of microbicides*. HCPs were asked about cultural, political, religious and social; literacy and communica-tion barriers between researchers and the target commu-nity; there willingness to counsel clients; challenges in promoting method in clinics and adequacy of staff resources.

Section D was concerned with *marketing strategies for microbicides*. Questions were asked regarding the most appropriate media communication channels, opinion leaders and communication agents, ideal times for pro-motion, preferred venues for obtaining microbicides, packaging preferences, and cost.

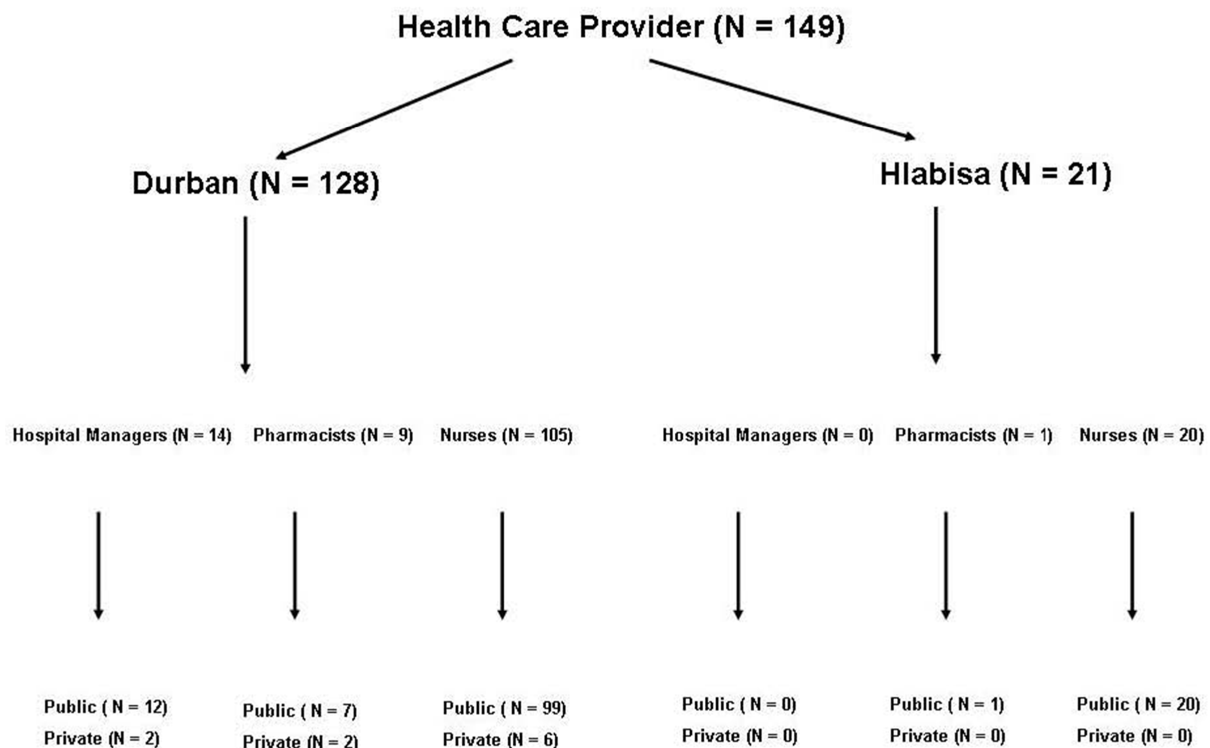

Figure 1. Study population and settings.

All HCPs were asked the same questions on demographic details in section A. For section B, questions were the same across job strata with a few exceptions:

(a) Nurses and Pharmacists were further questioned on whether they would recommend microbicides to PUs if they were 'as effective as condoms' and 'less effective than condoms'.

(b) The interviewer probed nurses and pharmacists on the question dealing with a potential microbicide that is 'less effective than condoms', by asking if they would recom-mend such a microbicide (i) with or without condoms;

(ii) to be used more often without a condom; (iii) and alternate between condoms and microbicide.

For section C, questions were tailored to provide informa-tion on how HMs would deal with obstacles facing their hospitals, staff and clients, in the event of a large-scale microbicide roll-out. With pharmacists, questions regard-ing the challenges of product placement and effective dis-pensation were emphasized. With nurses, different questions in this theme were asked to gain insight as to how they would counsel and educate PUs about using a potential microbicide, and the challenges that may go with it.

Section D on marketing strategies asked the same ques-tions, and was targeted towards pharmacists and nurses only.

Focus group discussions

The FGDs were conducted among CPNs using questions similar to the open-ended questions from the SSI questionnaires. The following questions and themes were explored:

(a) Information about microbicides.

(b) Microbicides as an STI/HIV prevention method.

(c) Groups of PUs to which the microbicide

should be dis-pensed to.
(d) Factors that affect the dispensation of microbicides in the health sector.
(e) Preferred marketing strategies in the introduction of the microbicide to the public.
(f) The most effective strategy to provide information to the clinic.
(g) If microbicides were introduced in the health care sys-tem, how would you like them to be introduced in clinics and hospitals?
(h) How should microbicides be packaged?
(i) Dispensation of the products in the pharmacy.
(j) If microbicides were to be dispensed in stores, where should it be displayed?
(k) If microbicides were introduced, how would you want PUs to obtain them?
(l) The acceptability of products to PUs.

Data analysis

Quantitative data from the SSIs were entered into an Epi-Info™ Version 6.4D database and checked twice prior to analysis with SPSS™ version 11.5. Data frequencies and tables were prepared and content analysis of the responses to the open-ended questions in the SSIs and FGDs was performed to identify and code salient themes, which were thereafter analyzed quantitatively using SPSS™ ver-sion 11.5. During content analysis, new codes emerged inductively following reading of the data. The codes were developed independently by research staff, who held meetings to achieve consensus about the coding catego-ries and met regularly to resolve discrepancies.

The SSIs and FGDs were conducted by bilingual Zulu-Eng-lish research staff with experience in conducting qualita-tive and quantitative interviews. Research staff were trained by senior study staff. All interviews were audio-recorded to ensure accuracy and quality of data and were transcribed verbatim.

Results

(1) Socio-demographic characteristics of participants

The 149 HCPs consisted of 14 HMs, 10 pharmacists, and 125 nurses. Ninety four percent (140/149) were female and from the public sector (93%, 138/149), with 78% (116/149) being of African descent. All of the HMs, 90% (9/10) of pharmacists and 84% (105/125) of nurses were from Durban. The remaining single pharmacist and 16% (20/125) of nurses worked in Hlabisa. Most of the HCPs (87%) followed the Christian faith.

In terms of type of practice/facility, 57% (71/125) of nurses worked in primary health care clinics, whilst 28% (35/125) worked in comprehensive facilities. The remain-ing 15% (19/125) of nurses were spread between family planning clinics, sexually transmitted diseases clinics and the like. For pharmacists, half of them worked in a clinic environment, whilst the remaining 50% (5/10) worked in commercial pharmacies. For the HMs, 78% (11/14) worked in primary health care environments, whilst the remainder came from other hospital settings.

(2) Health care providers descriptions and opinions about microbicides

Description's of microbicides

This aspect of the study was undertaken to assess HCPs ideas and beliefs about what microbicides were, including descriptions of physical features and intended purpose. Fifty-seven percent (8/14) of HMs, 40% (4/10) of phar-macists and 35% (44/125) of nurses had heard about microbicides before. Most participants had acquired this information in the previous year (2003), and primarily from the HPRU's training and community entry pro-grammes that are run throughout the province. A broad and simple definition of microbicides was also provided on the SSI questionnaire itself as follows:

"A microbicide could be used with the male and female condom for extra protection.

Some people may choose to use them without condoms. There are many factors that will impact on women's decisions to use these sub-stances".

HMs with prior information of microbicides had a vague understanding of the candidate products, and described them as a '*cream [that] prevents STIs*; a *cream [that] prevents pregnancy*; *they will kill...microorganisms*.' However, some were able to describe microbicides in more specific terms

– '*can be used as a protection against STDs even AIDS* and...*applied in the vagina by an applicator before sexual inter-course*.'

Whilst the 40% (4/10) of pharmacists with prior informa-tion of microbicides had a better understanding when compared to HMs, only one pharmacist (1/10) was aware that the active ingredient in microbicides is still unknown, given that all the products are currently in the testing phase.

Nurses who had prior information of microbicides as a potential HIV prevention method were reasonably accu-rate in their descriptions of candidate products – '*a gel...applied by females to prevent sexually transmitted infec-tions*.' One nurse expressed the following unsettling view about microbicide research: '*The rumour was that they* (researchers)*will ask you to sleep with a positive person* (HIV)*to prove whether it works*.'

Microbicides as a prevention method and empowering tool for women

Hospital managers saw potential microbicides as an empowering tool for women, recognizing that a person could '*make a decision alone without having to involve the partner*' and that '*men are resisting using condoms'*. Pharma-cists said that they were '*an excellent idea*, *convenient* and *good but not guaranteed to be used without a condom because a condom is used for more than one purpose*, here referring to the advantage of contraception that condoms have over potential microbicides, where the latter may or may not be indicated for contraception. Most nurses recognized that microbicides potentially could empower women, '*especially in our Black culture*' and corroborated the view that '*males don't want to use condoms*'. One nurse supported microbicides '*as long as* [they are] *not going to be messy'*.

Fifteen nurses were uncertain of their feelings about potential products. Only four of the 94 nurses who had prior knowledge about microbicides had negative opin-ions of them, challenging their potential acceptability and effectiveness. This was reflected in the following state-ments:

'If [a]*sex worker uses it, how effective is it going to be for her to carry it in her purse? Cultural beliefs may be a restriction.'*

'I don't think it will work or...be acceptable...because I thinkthe gel is messy'.

'I cannot guarantee it might prevent [HIV]*since it's in a gel form. Gel is usually slippery'*.

'Sexual investigations proved HIV not to be manageable. No hope at all.'

Access to microbicides

Most HCPs (77%) thought that microbicides should be dispensed to sexually active people whether infected or not with HIV and other STIs. One hospital manager felt this way because 'everybody is potentially HIV-positive until proven otherwise'. One pharmacist thought that since many people do not disclose their HIV status to their sexual partners, it would be better to give everyone access to microbicides. Nurses who wanted to dispense the prod-uct to all people believed that HIV positive people should have access to microbicides to prevent re-infection, decrease HIV/STI transmission to others, and prevent the acquisition of other STIs. For non-infected people, pri-mary prevention of HIV infection was the rationale behind the choice.

The remaining 23% of the HCPs felt that only some groups of people should receive the product when it becomes available. One HM felt that it could be detrimen-tal to administer microbicides to

those already infected because: '*if given to HIV-infected, people will have myths and mistake the product with the cure and start doing anyhow when it comes to sexual issues*', *i.e*., sexual promiscuity may result. One pharmacist advocated microbicides for those infected with STIs – '*A STI patient is a candidate for HIV. If you do not treat, STIs, increases...chances of...HIV.*'

Whilst the majority of HCPs felt that no age restriction should be implemented when microbicides are intro-duced, 17% (25/149) of them believed differently. Some HCPs who supported a no restriction policy felt that ado-lescents should be targeted because they are '*sexual* [ly]*active with more than one partner*'. Pharmacists agreed with promoting microbicides to all people of all ages, pro-vided that the '*generic composition of the product...is safe*' for all age groups. These HCPs had strong sentiments regard-ing the issue of HIV and sexual behaviour among young people :

'*HIV* [is]*not restricted to any particular age*'. [HM]

'*Cannot put age restriction because even the 12-year-olds are sexually active*'. [HM]

'*Sometimes you find a very young boy doing sex with a very young girl only to find that the condom does not fit this boy*'. [Nurse]

'*It [potential microbicide] should be given to anyone willing to use it*'. [Nurse]

The HCPs who supported age restrictions on access (17%) felt that youth might abuse microbicides and not take fur-ther precautions to prevent disease transmission. Others among this group felt that they should be reserved for adults '*because...you want to encourage abstinence for the young person*'. A pharmacist pointed out that they were '*not allowed to dispense to minors below 14 years otherwise we need informed consent.*'

Promoting microbicides as a partially effective prevention method, and condom use

When asked if they would recommend potential microbi-cides if proven to be less effective than condoms, 80% (8/ 10) of pharmacists and 75% (93/125) of nurses responded in the affirmative. The majority of these HCPs believed some disease protection was preferable to none. Pharmacists indicated they would recommend a microbi-cide which was less effective relative to a condom because '*safer sex is better than unprotected sex*;*for the safety of the female*' and because '*a microbicide is not visible*', unlike the female condom. However, most pharmacists stated that in this case they would prefer to recommend '*both the gel and condom*'. One pharmacist who would not recommend a microbicide of partial efficacy preferred to '*improve the product so that it can have the desired effect*'. The same phar-macist did indicate, however, that a cheaper product which '*may not have the entire effect*' may still have to be recommended. Nurses, even those who responded nega-tively to the question, endorsed the recommendation of both methods for '*dual protection*'.

Among nurses in Hlabisa, 60% (12/20) reported that they would not recommend partially effective microbicides, whilst in Durban 19% (20/105) would not. One reason for this discrepancy was that half of the nurses in Hlabisa misunderstood "less effective" as "not effective at all", despite clarification by the interviewer. This is illustrated by the following examples:

'*It's a waste of time to recommend something ineffective*'.

'*No point in using something useless*'.

When asked if they would recommend microbicides to their clients if they were as good as condoms in preventing HIV and STIs, almost all nurses and pharmacists (~ 100%) were unanimous that they would. Some of the reasons offered were:

'*HIV is a priority these days and is threatening everyone...We are willing to use the best product that we can get*'. [Pharma-cist]

'Any drug that has positive therapeutic benefit, is a drug of choice'. [Pharmacist]

'Because our aim is to fight against HIV and STI's'. [Nurse]

While agreeing to recommend them, one nurse noted that the decision to use them would be left to the client: *'In the same way that we promote condom usage, we will do the same to the gel. We will give clients the option to choose'*.

Negative perceptions of condoms and the advantages of microbicides over condoms were cited as further reasons to recommend potential microbicides of equivalent effi-cacy as condoms. Concerns about efficacy for pregnancy prevention, breakage, allergic reactions, and non-use were reported as impediments to condom use. In fact, 24% (30/125) of nurses mentioned the disadvantages of con-doms and that their clients did not want to use them. In contrast, microbicides were seen as easy to use, providing an alternative prevention option and enhancing sexual sensation, as reflected in HCPs' comments below.

'People find it difficult to put on condoms and [it]*does not take time to apply anything into the vagina. A female can do it prior* [to]*...sexual intercourse. It provides protection without forcing the other partner to use a condom.'* [Pharmacist]

The one nurse who was against recommending potential microbicides of equivalent condom efficacy felt that [she]*'can only ask for a person to choose to use either of the two'*, *i.e.*, in support of informed client choice.

Spreading the message for microbicide usage

Almost all (99%) of the 149 HCPs verbalised that their colleagues would be willing to recommend potential microbicides to clients if proven effective for HIV preven-tion. One HCP said that *'HIV infection is a problem. We do discuss our programmes. We evaluate our programmes. We test people at this clinic. If there are any means that...can be done to prevent this we should try it'*. Another stated that she wished to *'supply all the information so that the person takes an informed decision'*.

One pharmacist felt that 'a *nything to prevent the disease should be used. HCPs should be more knowledgeable about these. They need training so that they can spread the word around'*. Two of the 10 pharmacists indicated that *'the cost factor'* was important, microbicides should be *'economical for clients'*. Overall, a great majority of nurses would sup-port *'anything to prevent the disease because it is a kille*r and *we see what ...HIV is doing to the patients every day'*.

All of the nurses and pharmacists reported that they were willing to counsel clients about using microbicides for HIV/STI prevention. Nurses saw counseling as their *'duty'* and *'more effective than just issuing without counseling'*, *i.e.*, dispensing microbicides without providing information about them. Many nurses pointed out that since they counseled patients about condoms, they would do the same with microbicides, encouraging clients to make *'informed choices'*. One pharmacist commented: *'The more knowledgeable people are about medication, the more rationally it will be dispensed'*.

(3) Barriers to and facilitators for the introduction of microbicides in the public health setting

Potential barriers

Twenty one percent (3/14) of managers, 70% (7/10) of pharmacists and 62% (76/125) of nurses anticipated var-ious barriers to the introduction of microbicides. We clas-sified types of barriers as political, religious, cultural, level of literacy, miscommunication between researchers and community, time, resources, training needs, and other.

Managers were concerned about service providers not being properly informed about the product, as reflected in the following statement:

'It means that before the product is introduced they would have to be informed,

given lectures and it is only then that they (HCPs) may try and promote it'

One manager mentioned specific problems at his health care centre:

'*We do not have an antenatal or post natal facility nor do we have a family planning clinic*'

Presumably, a lack of such facilities would act as an obsta-cle to microbicide delivery. Other concerns that HMs had are reflected in these quotes below:

Pharmacists worried about the following issues:

'Tendering government pharmaceutical stores. If you haven't got the government system, it will delay the process'.

'Prescribers may not want to prescribe if the demand is too high'.

'A person may never anticipate when he/she is going to have sex'.

Pharmacists also noted that microbicides might be prob-lematic for users and partners who prefer inserting intra-vaginal substances for dry sex.

Among nurses, many indicated that men, especially among those who are of African descent, would not con-done women taking control over sexual matters. One social barrier noted was that '*the public may be skeptical'* about microbicides. Some nurses felt that educating peo-ple about microbicides would be difficult if they were not provided with '*enough information'*.

Many nurses cited a shortage of staff and limited space as barriers. '*Nurses' attitude* [s]*towards microbicides...if...nega-tive'* also was perceived to be an impediment. Cost was perceived to be a potential barrier, with some participants anticipating that microbicides will cost more than con-doms.

Nurses were further asked about possible challenges in promoting microbicides to patients in the clinics. In addi-tion to cost and limited staff resources, other challenges noted were limited availability and sustainability of prod-uct in clinics; potential user embarrassment (e.g., '*It might be difficult to demonstrate the use of this product'*), shyness, and/or discomfort in using a new method; lack of infor-mation and knowledge about the product, particularly regarding effectiveness; cultural myths; beliefs about product efficacy (e.g., '*The people...thinking that this product will cure HIV')* and male partners' reactions (e.g., '*If we are giving it to females, we don't know how her partner will react').*

However, many nurses did not anticipate any challenges to microbicide introduction in clinics – and believed '*that the patients will be happy to have access to this product'*.

Resources for distribution

Among nurses and pharmacists, nearly all (97%) felt that their facilities were properly situated for microbicide dis-tribution. Those who disagreed were probed regarding what could be done to improve access – '*Usage of mobile clinics* and *Teams (health workers) doing home visits'* were suggested. Among the HM's, 29% (4/14) felt that their staff would be sufficient to handle the demands of prod-uct roll-out. To ensure adequate staff resources for this programme, the common sentiment among managers was that they would '*have to motivate for more staff from the department'*. One manager felt that '*government should pro-vide more staff whenever introducing new product [s]'* and that '*enough space to accommodate clients'* must be provided.

Hospital managers's were asked how they would intro-duce the new product to their staff. Most opted for in-serv-ice training workshops; whilst one manager suggested that '*somebody from the company that deals with the product should come and train staff'*. When asked how they would intro-duce clients to microbicides, managers recommended advertising and health education – '*Everybody who comes to the clinic should be informed'*.

Counseling for microbicide use

Nurses and pharmacists were asked to rate how effective certain groups and venues would be for counseling clients and

promoting a potential microbicide. Ninety percent (9/10) of pharmacists felt clinics would be highly effec-tive. When asked about chemists, schools, hospitals and NGOs, 60% (6/10) of pharmacists thought that these groups would be highly effective. Forty percent (4/10) of pharmacists, however, were uncertain about the role tra-ditional healers could play in counseling. Sixty percent (75/125) of nurses felt clinics would be a highly effective or effective venue for counseling users about microbi-cides, and a similar proportion (57%, 71/125) felt the same about hospitals.

(4) Marketing strategies for microbicides

Promotion venues

Nurses and pharmacists were asked to rate the effective-ness of various venues for marketing microbicides, includ-ing advertising *via* radio, newspapers, TV, leaflets, posters, taxi ranks, billboards, and retail outlets. Although most pharmacists considered all of the abovementioned strate-gies to be highly effective, they rated leaflets, taxi ranks, and retail outlets as less effective marketing strategies. About three-quarters of the nurses rated TV and radio advertising to be highly effective. Similarly, like the phar-macists, while each type of advertising was evaluated as highly effective by some nurses, advertising on billboards, in taxi ranks and retail outlets was viewed to be the least effective strategies. Nearly two-fifths (59%) of nurses felt that TV advertisements promoting microbicides should be screened during all hours of the day. Forty percent (4/10) of pharmacists agreed. However, another 40% (4/10) of the pharmacists and about 22% (28/125) of nurses felt that the most appropriate time for these promotions would be in the evenings. In terms of radio advertise-ments, similar proportions of pharmacists (80%) (8/10) and 77% (96/125) of nurses agreed that advertisements on radio promoting microbicides should be screened all of the time.

Promotion strategies

Nurses and pharmacists were asked how they would want microbicides to be promoted in hospitals and clinics and were given the following response options: family plan-ning programmes, one-to-one counseling by nurses, advertisements on posters in doctors' rooms, life orienta-tion programmes by clinics in schools, and leaflets in clin-ics. Eighty percent (8/10) of pharmacists and 87% (109/ 125) of nurses opted for all of the above.

Over-the-counter dispensing in pharmacies and retail stores

As shown in Figure 2, the majority of pharmacists (80%, 8/10) and nurses (51%, 64/125) would like microbicides to be available over-the-counter. Over-the-counter refers here to products being placed behind store/pharmacy counters, separate from being placed on shelves. In order for the product to be obtained from behind a counter, it would have to be requested for, whereas product place-ment on shelves can be anonymously retrieved without requesting help from any store/pharmacy attendant. Phar-macists and nurses who preferred over-the-counter dis-pensing were against doctors' prescriptions due to the added cost of a consultation fee and the frequent lack of availability of doctors. In addition, over-the-counter was preferred for '*counseling purposes – Advice on side effects and how to use the product*' can be given. One pharmacist had this to say: '*Maybe...everyone will be too shy to go and get it although this one seems like an expensive product so maybe over-the-counter*'.

Some nurses opted for doctors to prescribe the product because they felt that '*the doctor will explain to you how to use them*'. Those who preferred the product to be placed on the shelves preferred this '*so that people will not be embar-rassed ...asking for the gel*'.

Figure 3 indicates that the majority of HM's, pharmacists and nurses preferred microbicides to be displayed on the shelves

in retail stores. The HCPs saw this as a way to facil-itate access to the product and instructions (e.g., '*Because you can take your time and read the information about it on a box*'); and decrease discomfort (e.g., '*Some people may not be comfortable being seen and asking about the product.*

Shelves are private') One pharmacist suggested that micro-bicides be displayed '*near the dispensary area*' to legitimize it as being health-related and allow greater privacy.

A nurse who favoured the display of microbicides at the till thought that '*everybody can... see them when they are standing in the queue*' while another nurse noted that that a person might be motivated to pick up this product while they are waiting.

Packaging

HCPs acknowledged that the '*packaging must appeal*' to potential users. Some suggested that microbicides be packaged in a box, while others preferred tubes for safety (e.g., '*to prevent it from any other contamination in the atmos-phere*'. Some pharmacists advocated for user information and instruction leaflets and a clearly demarcated expiry date. Other pharmacists considered size (e.g., '*pack of tam-pons*') and, material ('*cellophane containers like those used for cooler boxes...for the protection of the contents*'), and environ-ment-friendly issues.

Nurses also suggested that '*the box should be small and sexy to fit a pocket or a purse and a moisture-proof container*' to prolong the expiry date.

Cost

Seventy percent (7/10) of the pharmacists and 86% (107/ 125) of nurses felt that microbicides should be provided free-of-charge so that '*all people will have access to them*'. Nurses also indicated that many people were unemployed and thus would be unable to afford microbicides unless they were free.

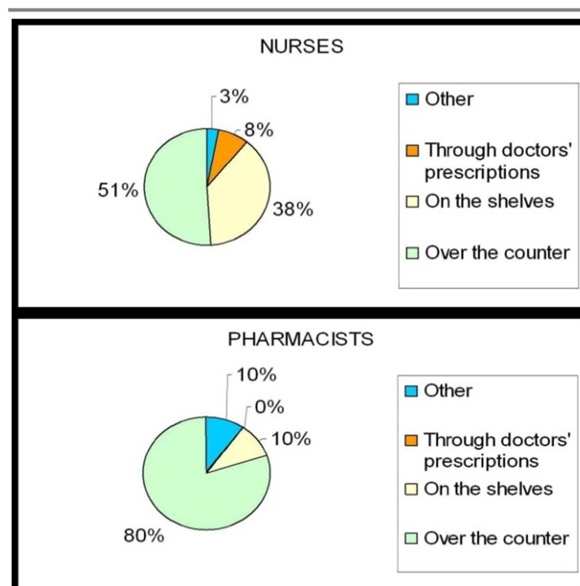

Figure 2. Preferences regarding dispensing of microbicides among pharmacists and nurses.

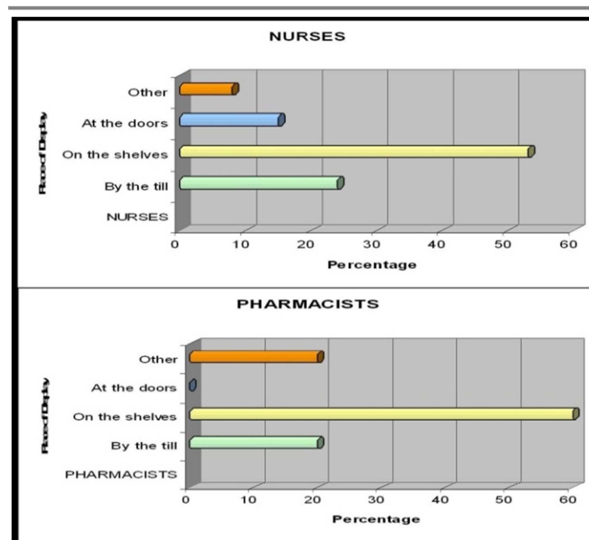

Figure 3. Preferences regarding the display of microbicides in stores among nurses and pharmacists.

The remaining 30% (3/10) of pharmacists felt that microbicides should be available both free-of-charge and for a fee – '*It can be both ways. For instance, con-doms are free in clinics and you can buy them at chemists for those who can afford* [them]'. One nurse who preferred patients to pay for microbicides was concerned that free

microbicides would '*encourage irresponsible* [sexual]*behav-iour'*.

HCPs were willing to pay as little as R1 to as much as R50 (about $0.17 to $8.33) for the product. R5 – R20 ($0.80 to $3.33) seemed to be an acceptable amount for most participants. One pharmacist felt that a free trial period could be beneficial. Microbicides should be free *'for the first two years because this is marketing. Scientists must commit* [by]*giving to our people. By so doing, they'll be making the product desirable to the community'*.

Discussion

HCPs who were primarily from the public sector serve most of the country. Therefore, their opinions on micro-bicides are of immense value. Approximately one third overall of HCPs were aware of microbicides. However, the depth of their knowledge varied. Whereas some had a good understanding of what microbicides are and their mechanisms of protection, others only knew that such products are being evaluated in research studies. Most knowledge of microbicides was acquired recently, indicat-ing the power of information dissemination through the MRC and other health professionals, and perhaps mount-ing support. Given that the first results of phase III trials for some candidates are expected in late 2008, it is imper-ative that as many HCPs as possible are educated about microbicides now so that when available, they will be familiar with and perhaps more open to the concept. As front-line providers, they are well-positioned to impart accurate information to their clients. Since clients often take HCPs into their confidence, they can play a valuable role in uncovering and challenging misconceptions about microbicides, e.g., that microbicide testing will involve deliberately exposing participants to HIV. Addressing these speculative myths now will help to build confidence and trust in the effectiveness of microbicides when they become available.

It was extremely encouraging that the vast majority of HCPs were positive about microbicides, and many felt that they should ideally be used in conjunction with con-doms. HCPs recognized the advantages that microbicides would have over condoms, especially for women, and nurses in particular described the lack of condom use among their clients.

Nearly four-fifths of all study participants felt that micro-bicides should be made available to everyone, regardless of age, HIV status, and history of sexually transmitted infections. HCPs recognize that they can no longer afford to restrict HIV prevention methods to certain groups because the entire population in South Africa is vulnera-ble, especially since rape and migrant labour contribute to the spread of HIV and AIDS. Nevertheless, some HCPs supported the restriction of access to microbicides due to concern that they would be seen as a "magic bullet" or cure, thus giving users a false sense of safety and perhaps license to engage in unprotected sex – an emergent con-cern with post-exposure prophylaxis [11]. In particular, restricted access to youth was noted.

The majority of HCPs reported that they would support microbicides if they are as good as condoms in preventing HIV transmission, especially because of the advantages that microbicides have over condoms. HCPs in this study were primarily concerned with the safety and size of the product applicator. If they are less effective, most pharma-cists and nurses reported that they would be more likely to support microbicides for dual method use, since a par-tially effective microbicide would still provide another prevention option for women [12]. A method that is less effective, but used consistently, may have a greater impact on reducing infection than a higher-effectiveness method used less consistently. In fact, mathematical modelling indicates that a microbicide which is 40% less effective than condoms, but is used only by 30% of the population, will save 6 million

lives the world over in three years [13]. HCPs should be informed of this fact as consistent use of future microbicides could be the key to decreasing the spread of HIV in South Africa.

Nurses, especially those in Hlabisa, demonstrated the sig-nificant effect that incorrect understanding can have on the perceptions of a product. A large number of them understood 'less effective' microbicides to be completely ineffective and as a result, did not want to recommend them to their clients. When such a product does become available, health care workers will need to be sufficiently trained regarding issues such as partial efficacy to prevent such errors. HCPs will need adequate information so that they are equipped to counsel patients in making informed choices.

The creation and dissemination of messages about micro-bicides now to HCPs will raise awareness of the potential of microbicides in reducing women's vulnerability to HIV and AIDS. In addition, early education will help to instill positive attitudes so that when an effective product comes to market, they will be prepared to counsel clients into using them. Since we anticipate that first-generation microbicides will likely have lower efficacy than con-doms, we should begin to design hierarchical prevention messages for HCPs to incorporate into client counseling, as well as testing their complexity and appeal.

Overall support for microbicides from HCPs was over-whelming and correlates with data reported in other stud-ies [14]. HCPs' dedication and sincere concern came across clearly in their willingness to counsel clients about microbicides and recommend the new products to others.

HCPs believed that the challenges facing the introduction of microbicides are extensive. Fewer HMs than nurses and pharmacists predicted barriers to the introduction of microbicides. This is significant because nurses and phar-macists are the ones who interact with patients and bring their issues across; therefore, their responses are probably a more valid reflection than those of the HMs. The obsta-cles foreseen ranged from cultural and religious beliefs to practical aspects, such as cost and characteristics of micro-bicides. Cultural practices are complex issues, and those such as the preference for dry sex and the importance of preserving a woman's virginity, will need to be addressed. The fact that microbicides will be novel was also raised, indicating that education of potential users will be neces-sary even prior to microbicides becoming available. Although health care facilities may be perceived as ade-quately prepared to handle the introduction of microbi-cides, additional staff resources will be required to address foreseeable shortages. Different health care centres will have their own challenges in rolling out the product and these will have to be dealt with on an individual basis. The relevance of these barriers mentioned by HCPs is that each challenge has the potential to halt the progress and use of microbicides. It is imperative, therefore, that plans are developed to overcome them, before the product is mar-keted for use.

Nurses and pharmacists were of the opinion that multiple organizations, such as hospitals, NGOs, other community organizations, and schools need to play a pivotal role in educating people about microbicides. Promotion of microbicides should take all forms. While the media was favoured as an effective marketing strategy, the written word was also perceived to be a credible source for deliv-ering health messages. Thus, both print and non-print media should be used to publicize microbicides.

Further issues involving marketing revealed that HCPs favour over-the-counter sales of microbicides at pharma-cies. This was to prevent added costs of consultation fees and so that patients will receive some counseling on the product. Adequate reasons were also provided on the pref-erence of

acquiring the product *via* a doctor's prescription or on the shelves. The same was noted for retail in stores – while the majority supported the display of the product on the shelves, others wished for them to be sold at the till. This indicates that multiple points of sale are probably the best option, but issues such as privacy, counseling and easy access need to be considered. Participants in a national US study reported that the ideal microbicide should be available in pharmacies without prescription and wanted someone to assist them in how to use the product (Darroch & Frost, 1999). However, most partici-pants preferred microbicides to be free-of-charge; although some were concerned that free products would be perceived to be of inferior quality, which has been noted about free distribution of male condoms.

Limitations

There were a number of limitations to the current study. Firstly, the majority of the study participants were women, reflecting the gender of most HCPs in South Africa's pub-lic health sector. Thus, whether male HCPs' beliefs and attitudes about microbicides differ from those of their female counterparts cannot be determined in this study. Study participants were self-selected volunteers, but selec-tion bias was minimized as only a few of those approached refused to be interviewed individually or *via* a focus group. HCPs' responses to microbicides were based on hypothetical products, and could differ once an effec-tive microbicide is identified.

Conclusion

This the first comprehensive study to explore HCPs knowledge and attitudes regarding microbicides. Our data illustrates important insights into HCPs' level of aware-ness and knowledge about microbicides and the potential challenges to be faced, in the event of their introduction. Understanding HCPs' preferences for marketing strategies will be invaluable to prepare microbicides for distribution and optimize their acceptability, uptake, and continued use. This information can also assist in short-term strate-gic planning for the crafting of appropriate prevention messages and identification of distribution channels and messengers for information dissemination. No single approach will be sufficient to reach the diversity of pro-vider and potential user target audiences.

Even in the absence of an efficacious product, increasing awareness of microbicides and their potential benefits and limitations will keep HCPs abreast of the current sta-tus of microbicide research findings. At the same time, continual evaluation of HCPs' current concerns, and after a microbicide is on the market, can correct misconcep-tions and help to shape positive attitudes and community norms about the possibility of this new women's HIV pro-tection product.

List of abbreviations

HCP = Health Care Provider

HM = Hospital Manager

PU = Potential User

CPN = Chief Professional Nurse

FGD = Focus Group Discussion

SSI = Semi Structured Interview

HIV = Human Immuno-deficiency Virus

AIDS = Acquired Immune Deficiency Syndrome

STI = Sexually Transmitted Infection

Competing interests

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

Authors' contributions

GR was the principal investigator of this study and wrote the grant, protocol and did the data analysis for the study with collaborations from NSM and JEM. NSM assisted in writing the paper, protocol writing, data analysis, pro-vided training and managed the team. JEM worked on the study grant and protocol, as well as provided reviews and input into the paper. JM assisted with the review and writ-ing of the paper. as well as coordinated the project, super-vised the field team and did quality control on the

data. JM also facilitated the data collection process, contacted the service providers and set appointmenets for the data collection. VG assisted with the data analysis, drafting of the paper and cleaning of the data sets.

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COLLAGEN REORGANIZATION AT THE TUMOR-STROMAL INTERFACE FACILITATES LOCAL INVASION

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Stromal-epithelial interactions are of particular significance in breast tissue as misregulation of these interactions can promote tumorigenesis and invasion. Moreover, collagen-dense breast tissue increases the risk of breast carcinoma, although the relationship between collagen density and tumorigenesis is not well understood. As little is known about epithelial-stromal interactions in vivo, it is necessary to visualize the stroma surrounding normal epithelium and mammary tumors in intact tissues to better understand how matrix organization, density, and composition affect tumor formation and progression.

Epithelial-stromal interactions in normal mammary glands, mammary tumors, and tumor explants in three-dimensional culture were studied with histology, electron microscopy, and nonlinear optical imaging methodologies. Imaging of the tumor-stromal interface in live tumor tissue ex vivo was performed with multiphoton laser-scanning microscopy (MPLSM) to generate multiphoton excitation (MPE) of endogenous fluorophores and second harmonic generation (SHG) to image stromal collagen.

We used both laser-scanning multiphoton and second harmonic generation microscopy to determine the organization of specific collagen structures around ducts and tumors in intact, unfixed and unsectioned mammary glands. Local alterations in collagen density were clearly seen, allowing us to obtain three-dimensional information regarding the organization of the mammary stroma, such as radiating collagen fibers that could not have been obtained using classical histological techniques. Moreover, we observed and defined three tumor-associated collagen signatures (TACS) that provide novel markers to locate and characterize tumors. In particular, local cell invasion was found predominantly to be oriented along certain aligned collagen fibers, suggesting that radial alignment of collagen fibers relative to tumors facilitates invasion. Consistent with this observation, primary tumor explants cultured in a randomly organized collagen matrix realigned the collagen fibers, allowing individual tumor cells to migrate out along radially aligned fibers.

The presentation of these tumor-associated collagen signatures allowed us to identify pre-palpable tumors and see cells at the tumor-stromal boundary invading into the stroma along radially aligned collagen fibers. As such, TACS should provide indications that a tumor is, or could become, invasive, and may serve as part of a strategy to help identify and characterize breast tumors in animal and human tissues.

Background

Tissue microenvironments play an important role in maintaining normal cell behavior [1-3]. Moreover, type I collagen is a prevalent component of the stromal extracellular matrix; its expression being spatially and temporally regulated during mammary ductal formation, suggesting it plays important roles in development [4]. Consistent with this idea, decreasing the levels of $\alpha_2\beta_1$ integrin, a primary type I collagen receptor, disrupts mammary epithelial tubulogenesis in vitro [2] and alters branching morphogenesis in vivo [5], respectively. Furthermore, inappropriate stromal-epithelial interactions can promote tumorigenesis [6-8], and in breast cancer, metastatic epithelial cells migrate in direct contact along stromal collagen fibers [9]. The importance of studying stromal interactions

in breast tissue is further reinforced by the fact that patients with collagen-dense breast tissue possess a greater than fourfold increased risk of breast carcinoma [10,11]. Although the mechanisms mediating the effects of the extracellular matrix (ECM) on breast carcinoma development in vivo are largely unknown, contributing factors may be adhesion mediated signaling and mechanical signals imparted on mammary epithelial cells from surrounding type-I collagen-rich stroma, either directly or across basement membrane proteins. One important step to elucidating these signaling interactions is to determine the organization of the collagenous stroma surrounding both normal mammary glands and tumors within intact tissue so as to better understand the cell-matrix interaction and how matrix organization, density, and composition affect tumor formation and progression.

Nonlinear microscopy techniques such as multiphoton laser-scanning microscopy (MPLSM) and second harmonic generation (SHG) provide powerful tools to image cellular autofluorescence and extracellular matrix structure in intact tissues [12-15]. Both techniques are well suited for high-resolution in vivo imaging, and second harmonic generation is particularly adept at imaging collagen structure. Specifically, multiphoton microscopy results from the nonlinear excitation of molecular fluorescence and can produce images deep into thick tissues [16,17], while SHG signals depend on non-linear interactions of illumination with a non-centrosymmetric environment (e.g. fibrillar collagen) that can provide submicron resolution [13-15]. The most commonly utilized multiphoton process is two-photon excitation (2PE) of fluorescence, in which two low-energy (usually near-infrared) photons simultaneously excite a fluorophore, which later decays to produce a single fluorescent photon of lower energy than the corresponding one-photon (half wavelength of 2PE) excitation [13,18,19]. In this 2PE process the fluorescence is dependent upon the square of the intensity (see Methods), producing optical sectioning that makes it equivalent to confocal imaging in terms of restricting excitation to the plane of focus, but facilitates a much greater effective imaging depth and better cell viability [16,20]. SHG imaging, on the other hand, does not arise from an absorptive process, but instead the laser field suffers a nonlinear, second-order, polarization when passing through certain ordered structures resulting in a coherent signal at exactly half the wavelength of the excitation [21]. Great utility arises from the fact that MPLSM and SHG can be implemented simultaneously in live tissue to provide complementary information and a powerful experimental and diagnostic tool.

The purpose of this study was to characterize collagen morphology in intact tissues so as to understand the structure-function relationship of epithelial- and tumor-stromal interactions in the mammary gland with particular emphasis on local tumor cell invasion during carcinoma progression. We used both MPLSM and SHG imaging, in conjunction with additional correlative microscopy techniques, to detect differences in local collagen density near normal glands and mammary tumors, and identify distinct collagen fiber organization around tumors, with characteristic collagen structures such as radially aligned collagen fibers associated with tumor-cell invasion. Identification and characterization of these collagen signatures sheds insight into the process of tumor cell invasion, and may serve a diagnostic capacity for determining the invasive potential of tumors.

Methods

Mouse mammary tissues and tumors

This study was approved by the institutional animal use and care committee and meets N.I.H. guidelines for animal welfare. To study non-tumor bearing mammary glands, tissue was obtained from B6129SF2/J mice or Col1a1^{tmJae} mice (The

Jackson Laboratory, Bar Harbor, ME, USA). To study tumor-stromal interactions in intact tissue, two mouse breast tumor models were utilized: MMTV-Wnt-1 (colony founder mice provided by Dr. Caroline Alexander, University of Wisconsin, Madison, WI, USA) and MMTV-polyoma middle-T (abbreviated PyVT following the Jackson Laboratory title but is also commonly abbreviated as PyMT or PyV-MT; colony founder mice originally obtained from Jackson Laboratory were provided by Dr. Amy Moser, University of Wisconsin, Madison, WI, USA).

Tumor explants and collagen gel culture

To study tumor-mediated collagen reorganization and tumor cell invasion in vitro, tumor explants were obtained and cultured in a manner similar to a previous report by Friedl and co-workers [22]. Small pieces of tumor were harvested from the central region of palpable PyVT tumors (that were confirmed by histology) with a 3 mm biopsy punch and were cultured in type I collagen gels. Following removal, tumors were rinsed in DMEM containing penicillin/streptomycin/fungizone solution (Cellgro, Herndon, VA). A single tumor explant was then cultured within a 2.0 mg/ml collagen gel (8.0 mg/ml rattail collagen solution (BD Biosciences, San Jose, CA) neutralized with 100 mM HEPES in 2 . PBS). Following Gel polymerization for 1 hr, the tumor explant containing collagen gels were released from the culture dish and floated in DMEM containing penicillin/streptomycin solution supplemented with 10% heat inactivated FBS. Imaging was performed on live (non-fixed) cells in intact three-dimensional collagen gels.

Multiphoton microscopy and second harmonic generation

Multiphoton excitation (MPE) with MPLSM allows imaging of endogenous fluorophores from deep inside live biological tissues with the fluorescence excitation primarily restricted to the plane of focus due to a quadratic dependence on the laser light intensity and a low probability of multiple low-energy photons being absorbed outside the focal plane [16,17,23]. For the case of a pulsed laser excitation, the time averaged fluorescent intensity is a function of the molecular cross-section $\delta_2(\lambda)$ and the square of the laser intensity, $I(t)^2$, and can be expressed as [23,24]:

$$\langle I_{f,p}(t) \rangle = \delta_2 \frac{P_{ave}^2}{\tau_p f_p} \left[\pi \frac{(NA)^2}{hc\lambda} \right]^2 \qquad (1)$$

In Equation 1, δ_2 is defined as a molecular cross section that represents the dependence for the probability of two-photon excitation on the square of photon density, P is the laser power, τ_p is the laser pulse width, f_p is the laser repetition rate, NA is the numerical aperture, h is Planck's constant, c is the speed of light, and λ is the wavelength.

In contrast to multiphoton excitation, which obeys the fundamental physical relationship of energy loss following excitation, SHG is a conserved polarization process that follows the relationship [21,25,26]:

$$P = \chi^{(1)} * E + \chi^{(2)} * E * E + \chi^{(3)} * E * E * E + \ldots \qquad (2)$$

where the polarization (P) and electric field (E) are vectors, and the nonlinear susceptibilities, $\chi^{(i)}$, are tensors. Therefore, SHG arises from the laser field suffering a conserved nonlinear, second-order, polarization when passing through non-centrosymmetric ordered structures that is described by term 2 of Equation 2.

For MPE and SHG imaging of live unfixed, intact (not sectioned), non-stained glands, and tumor explants within collagen gels, as well as hematoxylin and eosin stained histology slides, we used an optical workstation [27] that was constructed around a Nikon Eclipse TE300. For live tissue imaging, twenty mammary tissues including nine from the Col1a1^{tmJae} strain (three each of wild type, heterozygous and homozygous), and tumors from Wnt-1 (n = 10, plus wild

type controls) and PyVT (n = 20) mice were harvested and live tissue maintained in buffered media at 37°C. All tissues were imaged immediately following tissue harvest and a Ti:sapphire laser (Spectra-Physics-Millennium/Tsunami, Mountain View CA) excitation source producing around 100 fs pulse widths and tuned to 890– 900 nm was utilized to generate both multiphoton excitation (cellular autofluorescence from FAD) and SHG. The beam was focused onto the sample with either a Nikon 40. Plan Fluor oil-immersion lens (N.A. = 1.4) or a Nikon 60. Plan Apo water-immersion lens (N.A. = 1.2). All SHG imaging was detected from the back-scattered SHG signal [26], and the presence of collagen confirmed in our tissues using fluorescence lifetime imaging microscopy, or FLIM [12], on the same optical workstation, as the SHG from collagen has no lifetime. Additionally, due to the fundamental differences between MPE and SHG signals, filtering can separate the emission signals. Using a 464 nm (cut-on) long pass filter, MPE was discriminated from the total emission while a 445 nm narrow band pass filters was used to separate SHG (filters from TFI Technologies, Greenfield, MA). For 3D imaging in intact tissues, 2D (x-y) images were acquired at various serial depths (z) into the samples.

Acquisition was performed with WiscScan [28] a software acquisition package developed at LOCI (Laboratory for Optical and Computational Instrumentation, University of Wisconsin, Madison, WI, USA). Image analysis for combined MPE-SHG was performed with ImageJ [29] and VisBio [30] software. Using ImageJ, differences in collagen density were quantified by measuring the area of collagen signal following density slicing from a constant threshold, and local and mean intensity were measured within these normalized areas. For TACS-1 image analysis additional surface rendering plug-ins for ImageJ were utilized. For TACS-2 and -3, ImageJ was used to quantify the collagen fiber angle relative to the tumor. The tumor boundary was defined and the angle relative to the tangent of tumor boundary was measured every 10 microns.

Histology and electron microscopy

For histology, formalin-fixed paraffin-embedded samples from eight B6129SF2/J mice and eight Col1a1^{tmJae} mice were sectioned and stained for hematoxylin and eosin, trichrome, and picrosirius red using standard techniques. Additionally, all tissues imaged with MPLSM were subsequently fixed and processed for histology to confirm the presence of tumors and characterize the tumor morphology. Sample preparation for scanning and transmission electron microscopy (SEM and TEM, respectively) was performed by fixing whole mammary glands in 2.5% formaldehyde/2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer for 1 hr at room temperature (RT), after which sample were placed in fresh fixative overnight at 4°C. Samples were then washed in cacodylate buffer and postfixed in 1.5% osmium tetroxide at RT for 1.5 hrs. Samples (SEM n = 8 glands and TEM n = 6 glands) from B6129 mice were again washed in buffered solution and dehydrated, fractured, critical point dried, sputter coated, and imaged with SEM, or stained, dehydrated and cleared, embedded, and then sectioned for imaging with TEM [31].

Results

The normal mammary gland

Examination of the ECM surrounding mammary epithelial cells revealed that the majority of the stroma is fibrillar collagen, which was seen surrounding epithelial cells (Figure 1). Figure 1A, in which picrosirius red (a selective staining agent for collagen) was used indicates the presence of collagen around the mammary ductal structure (Figure 1A,B). Observations at high magnification with SEM showed collagen fibers wrapping around the ductal structure in an organized manner surrounding the epithelial cells (Figure 1C), in a fashion similar to that seen in Figure 1A. Additionally, collagen can be

seen wrapping individual cells in multiple directions (Figure 1C–E), suggesting a role for collagen as a containing and anchoring structure. Of further importance, higher magnification images with both SEM (Figure 1F,G) and TEM (Figure 1H) confirmed that the collagen fibers are composed of fibrillar collagen (Figure 1F; as indicated by their rod-like structure and presence of the ~67 nm banding pattern [32]) that are adjacent to the epithelial cells (Figure 1G,H). These data, in combination with published works indicating an important interaction between the stroma and the epithelial cell (see [4,5,33]), could suggest that these fibers apply physical restraint and mechanical signals across a thin basement membrane (<200 nm), or that the thin mesh-like basement membrane may contain some small gaps or membrane spanning cell processes and therefore may not completely isolate the epithelial cell; resulting in micro-regions of direct collagen-epithelial cell interactions [34]; or, most likely, a combination of both scenarios.

Although histology and electron microscopy provide valuable and detailed information regarding the composition and morphology of the epithelial-stromal interaction, these techniques are destructive to the sample and the capability for three-dimensional imaging is limited. Therefore, we have sought non-destructive imaging techniques (e.g. MPE/SHG) that allow imaging in four dimensions (x, y, z, and time). Combined MPE-SHG produced clear images of collagen (Additional file 1) as well as endogenous fluorophores, such as NAD(H) and FAD (Additional file 1, part C), in intact non-treated tissues [13,15,21]. Application of MPE/SHG to intact, non-fixed, non-stained mammary gland captured the morphology of the fibrous stroma seen in Figure 1. For example, images captured "above" the gland (Figure 2A: a and 2A: g) clearly showed the presence of wavy (crimped) collagen as well as the presence of taut (straight) fibril bundles (Figure 2A: a,e,f,g). Taut fibers showed a periodicity of ~250 nm (Figure 2A: c), consistent with previous reports for SHG resolution [14], which may represent an approximately fourfold super-periodicity of the basic ~67 nm banding pattern of collagen fibrils noted with SEM (Figure 2A: d). Additionally, collagen was observed wrapping around the epithelial duct (consistent with Figure 1A,C), as well as radiating away from the duct (Figure 2A: b). Furthermore, in addition to detecting unique features from normal mammary glands, examination of the epithelial-stromal interaction in Wnt-1 mice [35], which possessed ductal hyperplasia (Figure 2B: a–c), revealed abnormal mammary duct development with irregular collagen organization (Figure 2B: b,c). The ability to clearly discern these pathologic changes in tissues that were not fixed, sectioned, or stained (Figure 2B: d–f) validates the application of MPE/SHG imaging to detect normal mammary gland and collagen structure as well as abnormalities in mammary ducts and collagen distribution in situ (Figure 2B: f).

Detecting dense mammary tissue

High breast tissue density (due to increased collagen; [36]) is one of the single largest risk factors for developing breast cancer [37], yet the molecular mechanisms behind this high risk are not known. One reason for this deficit has been the lack of adequate animal model systems for studying the effects of increased collagen density in vivo. As such, we sought to identify an animal model system possessing collagen-dense breast tissue. Analysis of the col1a1^{tmJae} mouse model [38] revealed such a system. These mice possess a type I collagen mutation in the α1(I) chain, making them resistant to human collagenase, resulting in fibrosis of the skin and uterus due to excessive collagen accumulation [38]. However, increases in collagen deposition in the mammary glands of these mice have not been previously described. Analysis with standard histology clearly revealed increased collagen surrounding the mammary ducts in

both homozygous and heterozygous female mice regardless of parous status (Figure 3A vs 3C; Additional file 2). By utilizing histology and imaging hematoxylin and eosin (H&E) stained sections with MPLSM (SHG signal did not exist after formalin fixation; data not shown), the presence of increased collagen was confirmed (Figure 3B vs 3D), as well as an apparent hyperplasia in Col1a1 mice (Figure 3C,D; Additional file 2). Interestingly, this hyperplasia was associated with inva-sive-looking epithelial cells that resemble an epithelial-mesenchymal transition at the ductal end (Figure 3C,D).

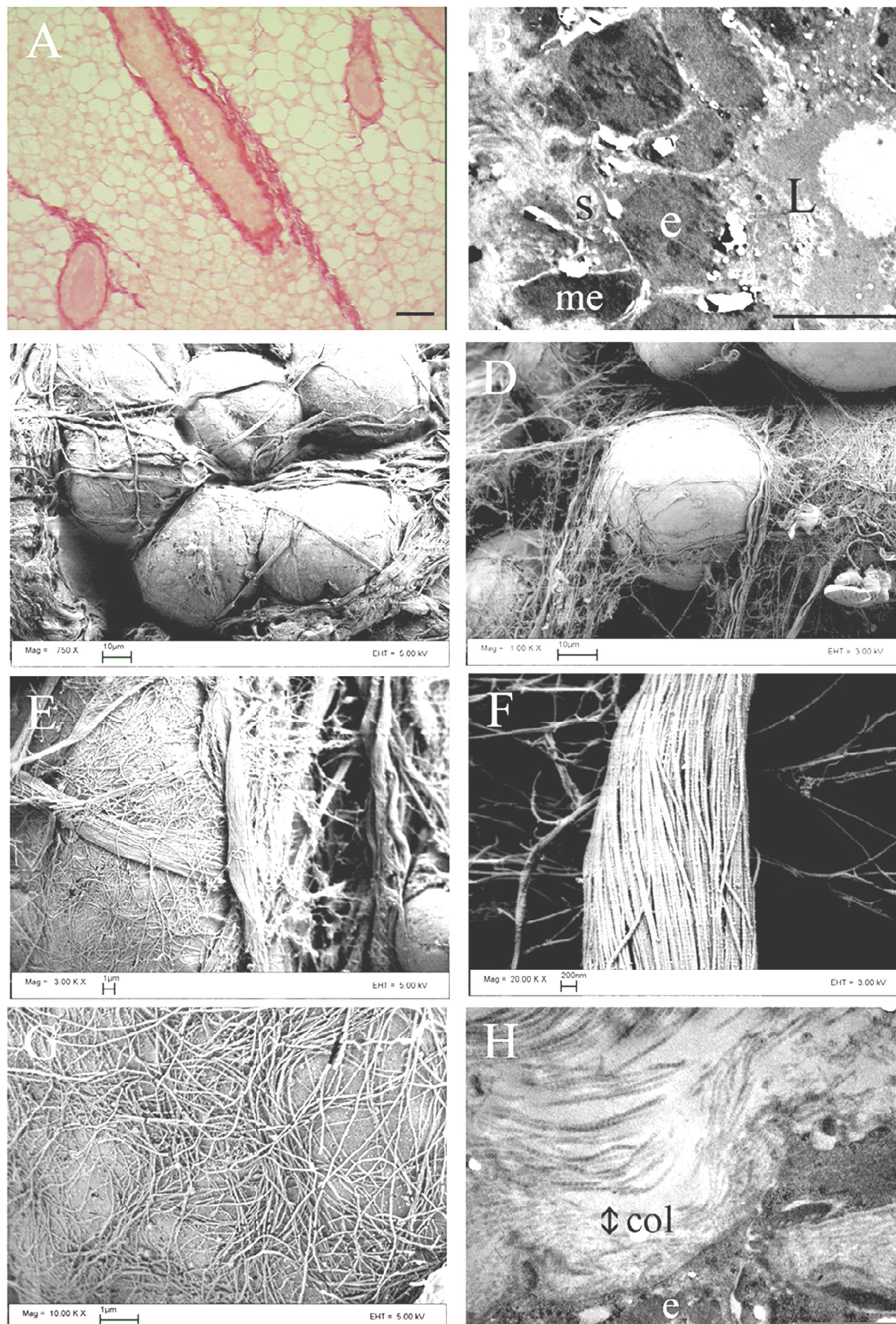


Figure 1. Collagen morphology and the epithelial-stromal interaction in the mammary gland. (A) Picrosirius red staining (red), a selective collagen stain, indicating the primary stromal component is collagen

(bar = 50 μm). (B) Low magnification (bar = 10 μm) TEM image of a mouse mammary duct (transverse section) showing the organization of epithelial (e) and myoepithe-lial (me) cells outside the lumen (L) in close association with the collagenous stroma (s), with myoepithelial cells not completely separating the stroma from the epithelial cells. (C) SEM image of the ductal end. (D) SEM image of collagen fibers interacting with ductal epithelial cells. (E) SEM image of collagen bundles wrapping around the cell in multiple directions. (F) Collagen fibrils possessing a rod-like structure with the characteristic ~67 nm banding pattern validating the presence of fibrillar collagen in proximity to epithelial cells. (G) SEM image of collagen fibrils immediately adjacent to the cell surface. (H) TEM image of colla-gen fibrils (col) next to the epithelial cell (e).

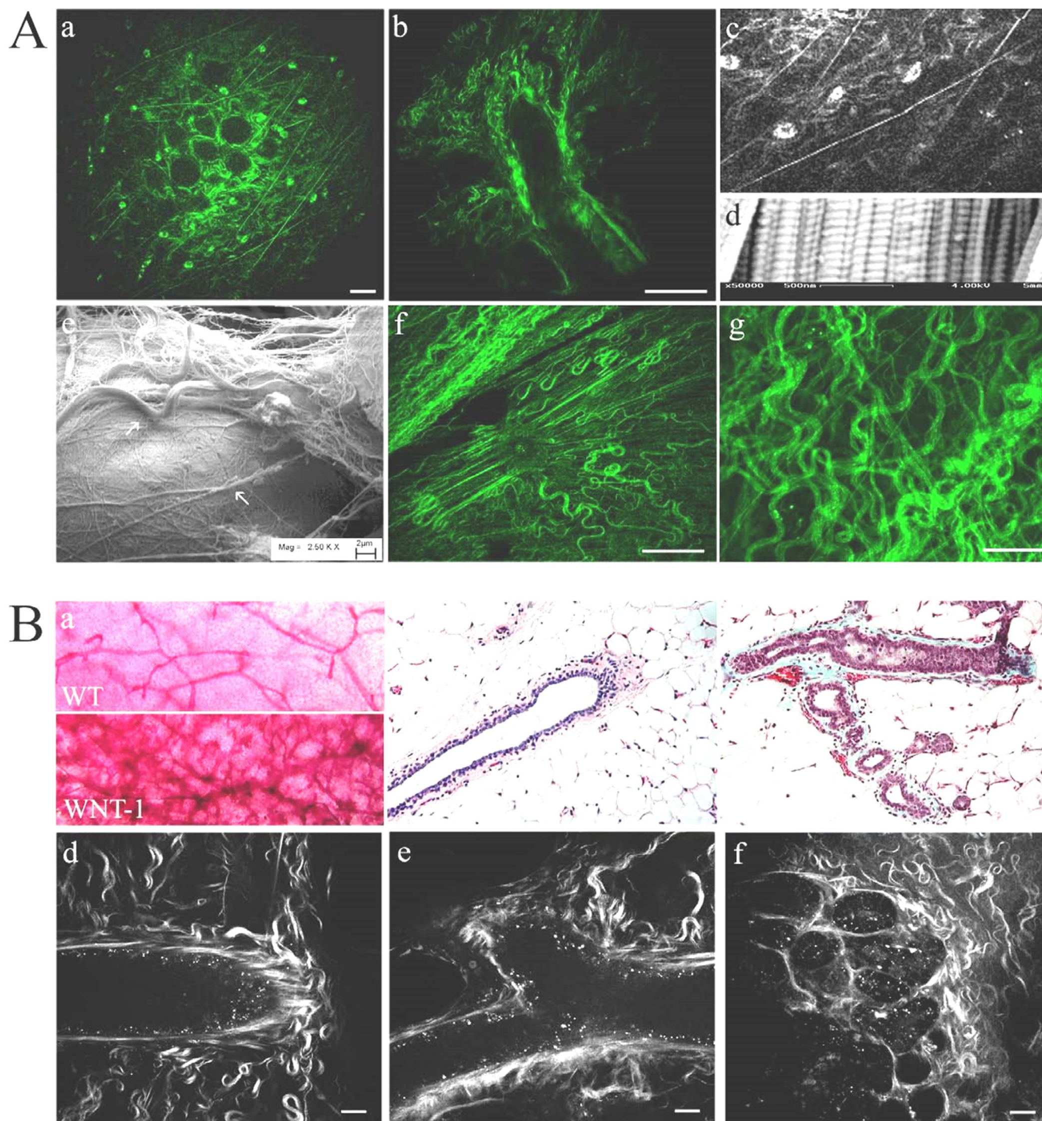


Figure 2. MPLSM/SHG imaging reveals native collagen structure in living mammary gland. A: (a) MPE/SHG image at the "top" of the mammary duct, showing both wavy and taut (straight) collagen structures as well as endogenous fluorescence from FAD in stromal cells (most likely fibroblasts and immune cells). (b) MPE/SHG image of a mammary duct demonstrating collagen wrapped around the duct as well as radiating out from the duct (as can be seen predominantly at the top of the micro-graph near the end of the duct). (c) Enlarged section from (a) showing some aspects of collagen fibril structure that resemble the standard banding pattern seen in collagen fibrils from connective tissue. (d) SEM of mouse tendon mouse tendon demon-strating the ~67 nm banding pattern characteristic of collagen fibrils. (e) Correlative SEM image of collagen surrounding ductal epithelial cells showing both wavy (upper arrow) and taut (lower arrow) fibers that match the collagen structures obtained with MPE/SHG imaging. (f) MPE/SHG image of the region near the nipple in tissue demonstrating

straightened collagen fibers radiating from the central ductal structure. (g) MPE/SHG image "above" the mammary duct showing both wavy and taut fiber structures. Note: all mammary tissues in A are from the B6/129 strain, which serves as the background strain for col1a1 mice.

B: (a) Whole mount analysis from wild type control (top) and Wnt-1 mice (bottom), which display hyperplasia compared to wild type glands. (b,c) Histology of mammary glands from wild type control animals (b; H&E) and hyperplastic abnormal ducts from Wnt-1 mice (c; Masson's Trichrome). (d,e) MPLSM/SHG imaging of wild type control mammary duct demonstrating a ductal end (d) and branching (e). (f) MPLSM/SHG imaging of a mammary duct from a Wnt-1 mouse showing hyperplasia of the ductal structure and increased deposition of disorganized collagen. Note: All MPE/SHG images are from live intact tissues that are not fixed, sectioned, or stained; scale bar for MPE/SHG images equals 25 μm; scale bar for histology images equals 50 μm.

Therefore, in an approach opposite to that taken by Jain and co-workers [39] where a decrease in collagen in vivo was detected with SHG, we detected increased collagen in live intact mammary glands. Analysis of glands from col1a1 heterozygous and homozygous mice, and associated wild type littermates, noticeably revealed increased collagen surrounding epithelial ducts from transgenic mice (Figure 3E–H), demonstrating our ability to detect differences in collagen density. Furthermore, collagen was locally dense adjacent to (wrapped around) the epithelium, as well as increased in the space extending from the duct resulting in a 2.53- (± 0.24) and 2.79- (± 0.34) (mean ± SEM) fold increase in the area of collagen signal, as well as increased signal intensity around the duct, for heterozygous and homozygous col1a1^{tmJae} mice relative to wild type animals, respectively. Therefore, the col1a1 mouse model appears to be a promising candidate for studying the effects of increased collagen density in normal as well as transformed epithelial cells as appropriately crossed heterozygous col1a1 mice are capable of forming tumors without inhibition from the collagenase resistant matrix

(P.P.P. and P.J.K unpublished observations). Moreover, we could discern changes in density and obtain images from deep (maximum Depth: 440 nm) within intact mammary tissue (Figure 3H; Additional file 4) without fixing, sectioning, or staining the tissues, suggesting that this approach could have wide application in live animal or tissue models for understanding stromal changes associated with pathologic conditions.

Tumor-associated collagen signatures (TACS)

Tumor-associated collagen signature-1

Analysis of tumor bearing Wnt-1 mice, which progress through hyperplasia, mammary adenocarcinoma, and invasive (metastatic) ductal carcinoma, revealed multiple epithelial clusters, containing hemorrhagic regions, intermixed and surrounded by increased collagenous stroma (i.e. desmoplasia), consistent with previous reports [35]. Importantly, the presence of increased collagen allowed us to identify pre-palpable tumors (Figure 4A: a–c, Additional file 5; and confirmed with histology – data not shown) by the existence of what we are classifying as one of three tumor-associated collagen signatures (TACS). Namely, TACS-1: the presence of dense collagen (Figure 4A: a), indicated by increased signal intensity (see surface map in Figure 4A) at a region near the tumor (Figure 4A: a; Additional file 5) that served as a reliable hallmark for locating small tumor regions. Although increased collagen has been reported near tumors, the structure of such collagen has previously been largely unknown, and the additional focal localization shown in Figure 4A indicates increased local areas of high density within the globally increased collagen concentration surrounding tumors. However, it is unclear whether: (1) a pre-tumor dense region is present that serves to stimulate tumor formation, (2) the dense

region of collagen is pulled into a grouped cluster through increased contraction of an epithelial tumor mass or motile cells at the tumor boundary, or (3) fibroblast activation results in increased local collagen deposition. Further analysis into this fundamental characteristic should provide useful information on tumor initiation and progression.

Tumor-associated collagen signatures-2 and -3

As the size of the tumor increased, we identified a second collagen signature, TACS-2: "taut" collagen fibers stretched around the tumor (Figure 4B). This collagen morphology likely arose from stretching of the stroma due to tumor growth, which may act to constrain portions of the tumor (i.e. compressive restraint) as well as provide a stretch induced tensile stress in expanded fibrils (and larger resistance to cell contraction in the stroma) that stimulates and activates fibroblasts. Evidence for tumor restraint in Wnt-t mice can be seen in Figure 4B, a–c, where collagen fibers are stretched around a relatively smooth tumor boundary as indicated by the fact that the fiber angle is primarily distributed tangentially (0° relative to the tumor boundary) along the tumor boundary (see histogram in Figure 4B).

In regions of tumor masses that are undergoing growth and invasion (Figure 4C: a–c), a third tumor-associated collagen signature, TACS-3, was identified: collagen fibers aligned normal to tumor boundary regions that display an irregular shape – indicative of local invasion through collective epithelial cell migration [22,40]. This invasive tumor morphology was seen in regions of tumors where collagen fibers are primarily aligned in the direction of cell invasion (see histogram in Figure 4C, in which the angle of the collagen fibers relative to the tumor boundary distributes around 90°). Furthermore, at regions where TACS-3 is noted, we observed groups of cells advancing from the tumor boundary in a collective manner that appear to be undergoing collective invasion [22,40,41], as well as individual invading cells that may relate to single cell migration similar to what has been observed along collagen fibers in an in vivo xenograft model [9].

To further investigate the behavior of the third collagen signature in a more invasive and metastatic cancer model, we utilized the well established and characterized PyVT mouse model. This model bears resemblance to many aspects of human cancer, is reliably invasive and metastatic following defined, progressive, and reliable histological grades from hyperplasia to adenoma, and then to early and late carcinoma, and therefore provides a good model for studying human disease [42]. Tumor cell behavior and collagen morphology in this model were similar to observations from the Wnt-1 mouse tumors. For instance, tracking the tumor-stromal boundary around individual tumors (Figure 5A–D) first revealed regions of TACS-2 morphology, in which restraining collagen wrapped around a relatively smooth boundary (Figure 5A,B, and histogram: TACS-2). In regions of TACS-2, cells had a mostly random alignment with a subset of cells aligned in the same direction as the collagen (Figure 5A,B). The second region revealed a TACS-3 boundary where collagen has been primarily aligned perpendicular to the tumor (Figure 5C,D, and histogram: TACS-3). A reasonable hypothesis for this behavior is that collagen fiber realignment occurs through morphogenesis and contractile events from cells at the tumor boundary, to organize the matrix and to prepare for local invasion (see Figure 6 for TACS-2 to -3 transition). Evidence for this hypothesis is seen by the collagen structure associated with regions of invading cells in the Wnt-1 tumors (Figure 4C), PyVT tumors (Figure 5A–D; Figure 6), and MPLSM analysis of invasive regions in tumor histology sections (Additional file 3).

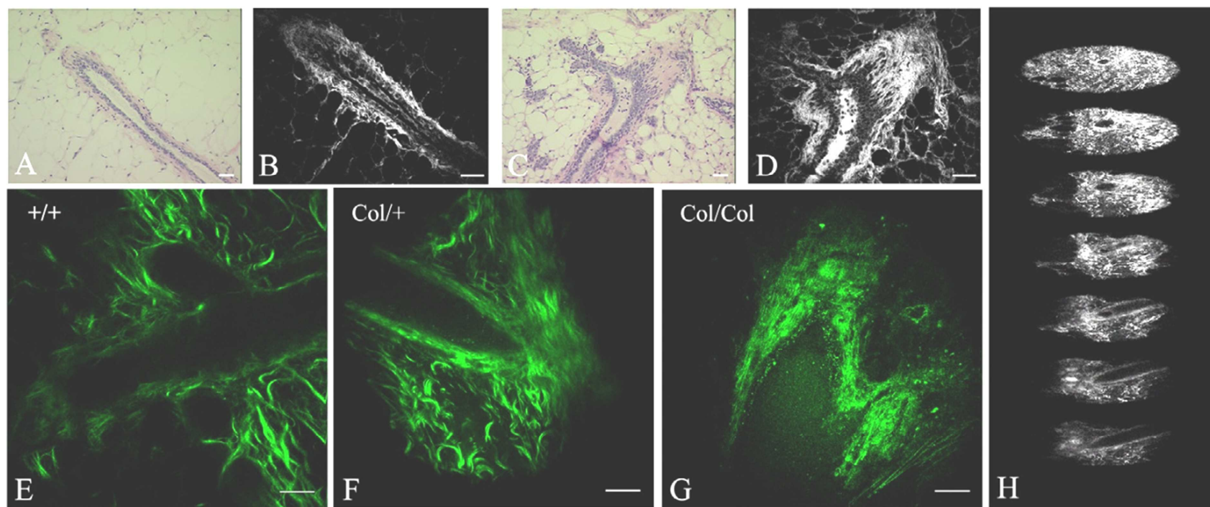
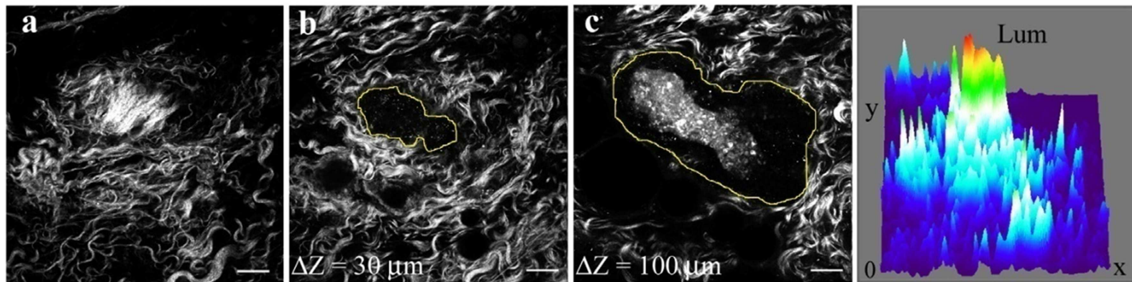


Figure 3. MPLSM/SHG imaging detects increased collagen density in the mammary gland. (A) H&E stain of wild type control mammary gland imaged with bright field microscopy. (B) MPE image of (A) showing the power of MPLSM to visualize collagen structure. (C) H&E stain of mammary gland from a col1a1/col1a1 homozygote mouse. (D) MPE image of (C) showing increased visualization of collagen density and structure and the irregular epithelial-stromal boundary, with epithelial cells invading into the locally increased collagen stroma. (E-G) MPLSM/SHG image of live mammary ducts that are not fixed, sectioned, or stained from wild type (E), heterozygous (F), and homozygous (G) col1a1 mice, showing increased collagen density in transgenic ani-mals. (H) Z-stack of (F) spanning 340 μm (typical depth capability 350–440 μm) illustrating the structure of the glands and their relative location in the gland (see Additional file 4). Note: scale bar for MPE/SHG images equals 25 μm.

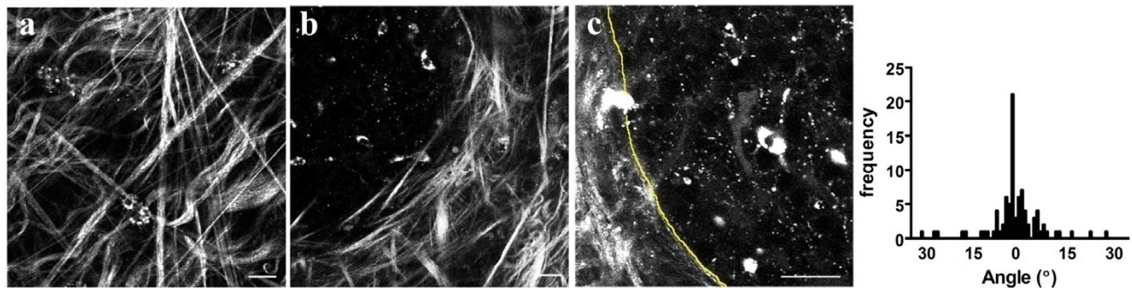
In all these cases local tumor invasion occurred where collagen fibers are aligned radially from the tumor in the direction of tumor cell invasion (see TACS-3 histogram in Figure 5, and the change in stromal alignment correlated with the change to invasive cell morphology in Figure 6). Additionally, some invading cells were in direct contact with fibers (Figure 5E,F; Figure 6C,D). In certain cases, some matrix disorganization was also observable (see Figure 4C: c and Figure 5E) possibly indicating proteolytic cleavage of collagen [40,43].

To further test the hypothesis that tumor cells realign the collagenous matrix to facilitate local invasion, we determined whether tumor cells could reorganize a random collagen matrix. Analysis of tumor explants within type-I collagen gels revealed radial collagen alignment at regions of tumor cell invasion into previously randomly aligned collagen gels (Figure 7), consistent with previous reports analyzing fixed tumor explants in 3D reconstituted matrices [22], and supporting information about invasion within intact live tissues (Figures 4, 5, 6). Following polymerization, circular collagen gels (disks) displayed a random orientation of collagen fibers (Figure 7A) without an outside force to initiate structural reorganization. Tumor explants cultured within such random collagen gels contracted and reorganized these collagen gels, resulting in various local outcomes with collagen wrapped around the explant at non-invading regions (Figure 7B). In contrast, at regions of invasion into the gels, collagen was reorganized to a radial alignment (Figure 7C) with direct contact between collagen fibers and invading cells (Figure 7C,D). This demonstrates that tumor cells can de novo reorganize a random collagen matrix to facilitate vivo.

A. TACS-1:



B. TACS-2:



C. TACS-3:

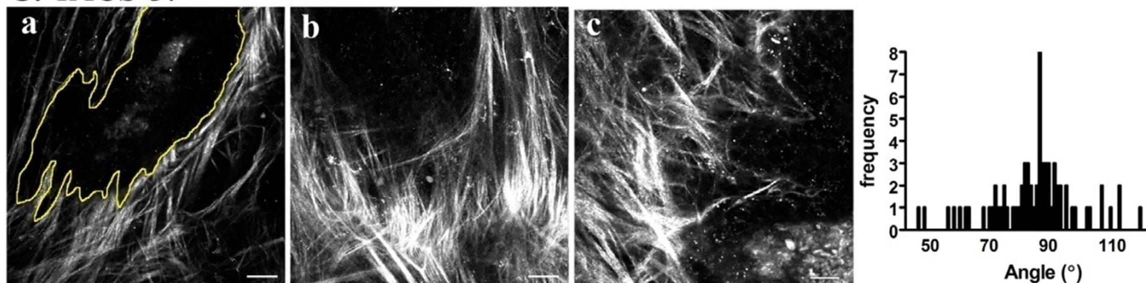


Figure 4. The tumor-stromal interaction: representation of the three TACS in Wnt-1 mouse tumors. (A-C) Micrographs illustrating the identified TACS. A: TACS-1. MPE/SHG image of TACS-1. Namely, a region of dense collagen (a, and surface map) "above" a non-palpable tumor (b,c; yellow outline) that is indicative of the presence of a small tumor (also see Additional file 5). The surface map quantifies the intensity of the fluorescent signal relative to x-y location, and clearly demonstrates an increased collagen signal, and is representative of six Wnt-1 tumors and eight PyVT tumors (not shown) B: TACS-2. MPE/SHG image of the second TACS indicated by the presence of straightened (taut) fibers characteristic of a larger Wnt-1 tumor. B: a-c, MPE/SHG images of collagen fibers in Wnt-1 mice stretched around a relatively smooth tumor boundary (outlined with a yellow line in c) as demonstrated by the fact that majority of the fibers are parallel to the tumor boundary. B: histogram, the angle of collagen fibers relative to a line tangential to the tumor boundary was measured for 86 regions in six independent tumors, and graphed as a frequency distribution resulting in a distribution of fibers around 0°. C: TACS-3. The third TACS: aligned collagen fibers at regions of cell invasion in Wnt-1 mice. C: a-c, he irregular tumor boundary associated with local inva-sion is outlined in yellow (in a) and connected to fibers that are primarily distributed normal to the initial tumor boundary, rep-resented by a frequency distribution around 90° relative to the tumor boundary. C: histogram, the angle of collagen fibers relative to a line tangential to the tumor boundary was measured for 71 regions in six independent tumors, and graphed as a frequency distribution resulting in a distribution of fibers near 90°. Scale bars equal 25 µm.

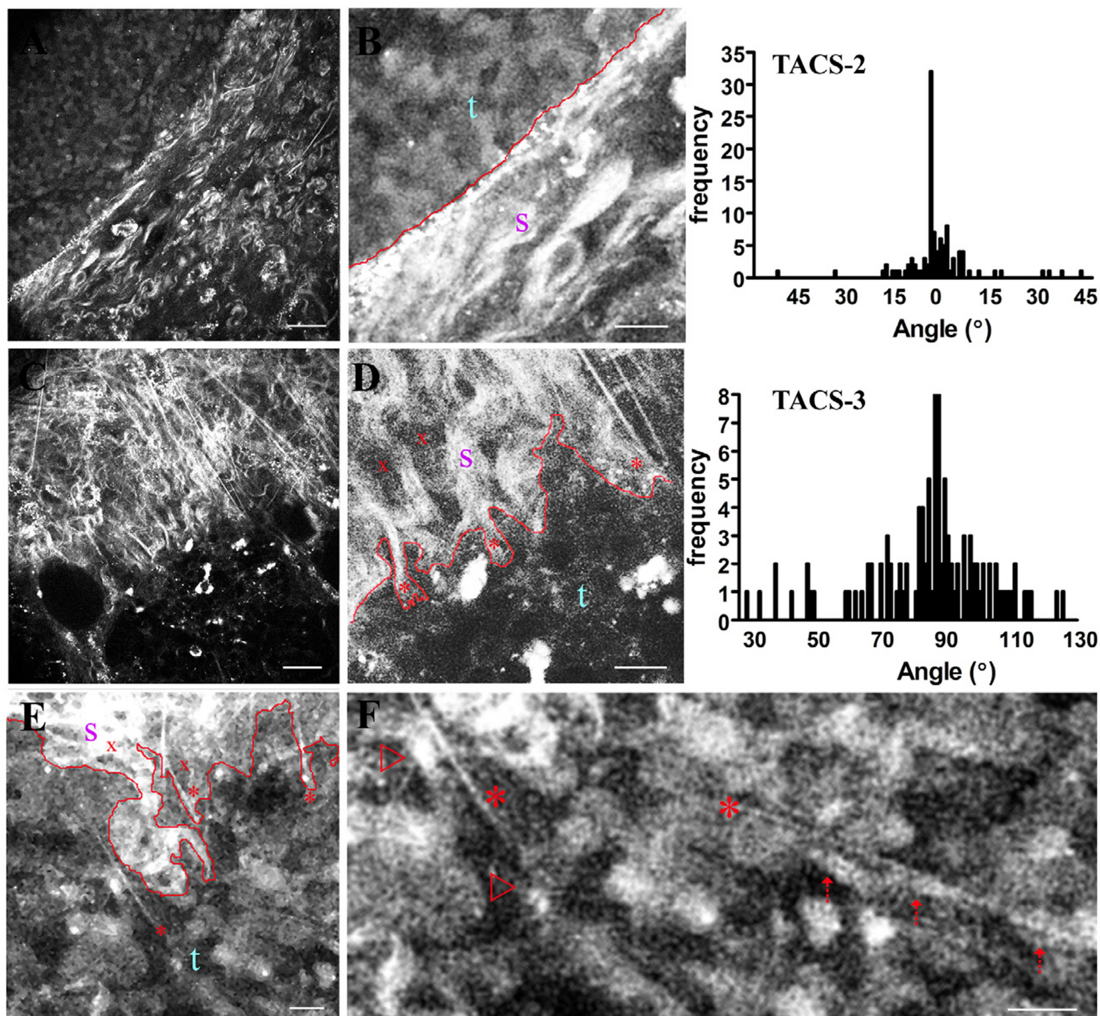


Figure 5. Study of TACS-2 and -3 in the more aggressive PyVT mouse tumor model. (A) TACS-2, with an enlarged cutout region (B) shown at higher brightness and contrast levels and a rough demarcation of the tumor-stromal boundary (red line; s = stroma; t = tumor) to further indicate the wrapping of the collagen parallel to the tumor boundary (distribution near 0°, see top right TACS-2 histogram of 106 regions from eight independent tumors). (C) TACS-3, with an enlarged cutout region (D) shown at higher brightness and contrast levels and a rough demarcation of the tumor-stromal boundary (red line; s = stroma; t = tumor). Note that although some cells have moved past this boundary (examples = x) into the fibers, the boundary serves as a general representation of irregular invasive region into radially aligned collagen fibers (frequency distribution around 90°, see middle right TACS-3 histogram of 109 regions from eight independent tumors). Furthermore, analysis of TACS-3 regions

(E) at higher magnification (F) show endogenous cells associated with fibers at the tumor-stromal boundary and within the tumor. * Indicates examples of fibers interdigitated with the invasive tumor boundary and in contact with the invading tumor cells (red arrows). Scale bar for MPE/SHG images A, C, E, and F equals 25 μm, and 10 μm for B and D.

Hence, our results suggest that in order to facilitate invasion, supporting the hypothesis that matrix reorgani-local invasion, cells at the tumor boundary contract and zation at the tumor interface facilitates local invasion in align collagen fibers, perhaps with the assistance of prote olytic cleavage to facilitate matrix reorganization, and then invade along aligned collagen structure to expand the tumor and later metastasize.

A.

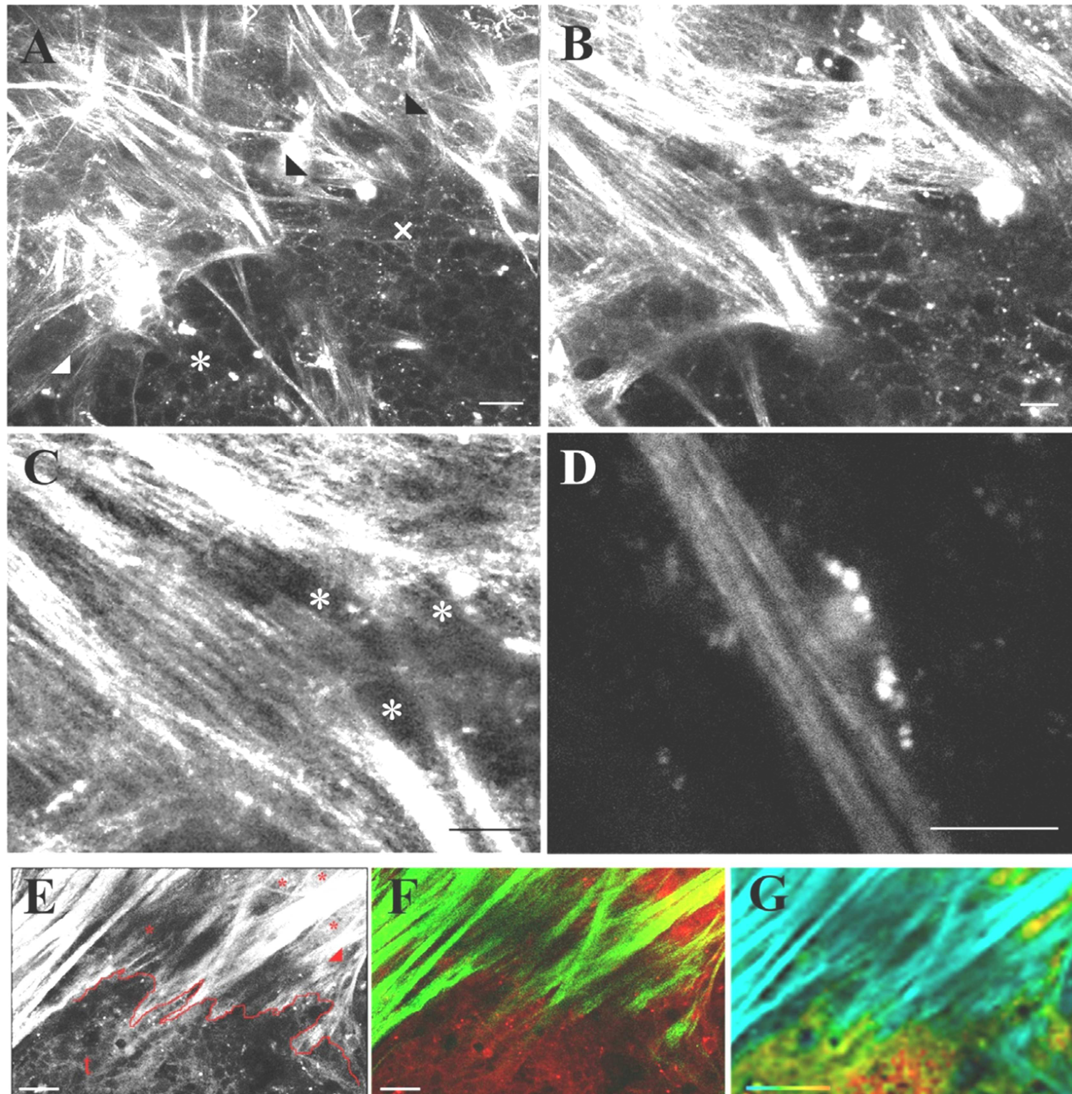


Figure 6. TACS-3 – radially aligned collagen fibers associated with invasion. Combined MPE/SHG imaging of live intact PyVT mammary tumors indicates that (A) non-invading regions (*) possess taut collagen (TACS-2; white arrowhead) wrapped around the tumor, while regions of invasion (x) are linked to aligned collagen, with cells invading along radially aligned collagen fibers (TACS-3; black arrowheads). Examination of invasion at the tumor-stromal interface at higher magnification (B and C) clearly reveals the collagen alignment at specific regions of invasion (B) with tumor cells (*) in between, and in association with, aligned collagen fibers (C). (D) Example of an individual tumor cell attached to a collagen fiber leading away from the primary tumor. Additionally, tumor cells that have invaded across the tumor-stromal boundary can be visualized by separating the MPE and SHG signals or imaging with FLIM. (E) Combined MPE/SHG image of a TACS-3 region facilitating local invasion. The tumor-stromal boundary is not well preserved at this stage, but is roughly outlined in red. Examples of regions of cells that have invaded past the boundary are marked with an asterisk (t = the primary tumor). The red arrowhead indicates cells near the tumor boundary that are migrating along aligned collagen fibers away from the primary tumor. (F) MPE and SHG signal separa-tion of the image shown in E. MPE signal is represented in red pseudo-color while SHG is shown in green pseudo-color. Note the interdigitation of aligned collagen fibers (green) into the tumor, with individual, or lines of, cells (* in E) migrating away from the tumor on collagen fibers. (G) FLIM micrograph of invading cells at the TACS-3 region shown in E and F. Collagen (blue; no fluorescence lifetime) can be distinguished from cells (green to yellow), confirming the presence of invading cells at the tumor-stromal boundary and cells that have migrated past the boundary in association with collagen. The color bar in G ranges repre-sents the weighted mean ranging from 100 ps (blue) to 1 ns (red). Scale bars equal 25 μm in A, E, F, and G; 10 μm in B, C, and

D.

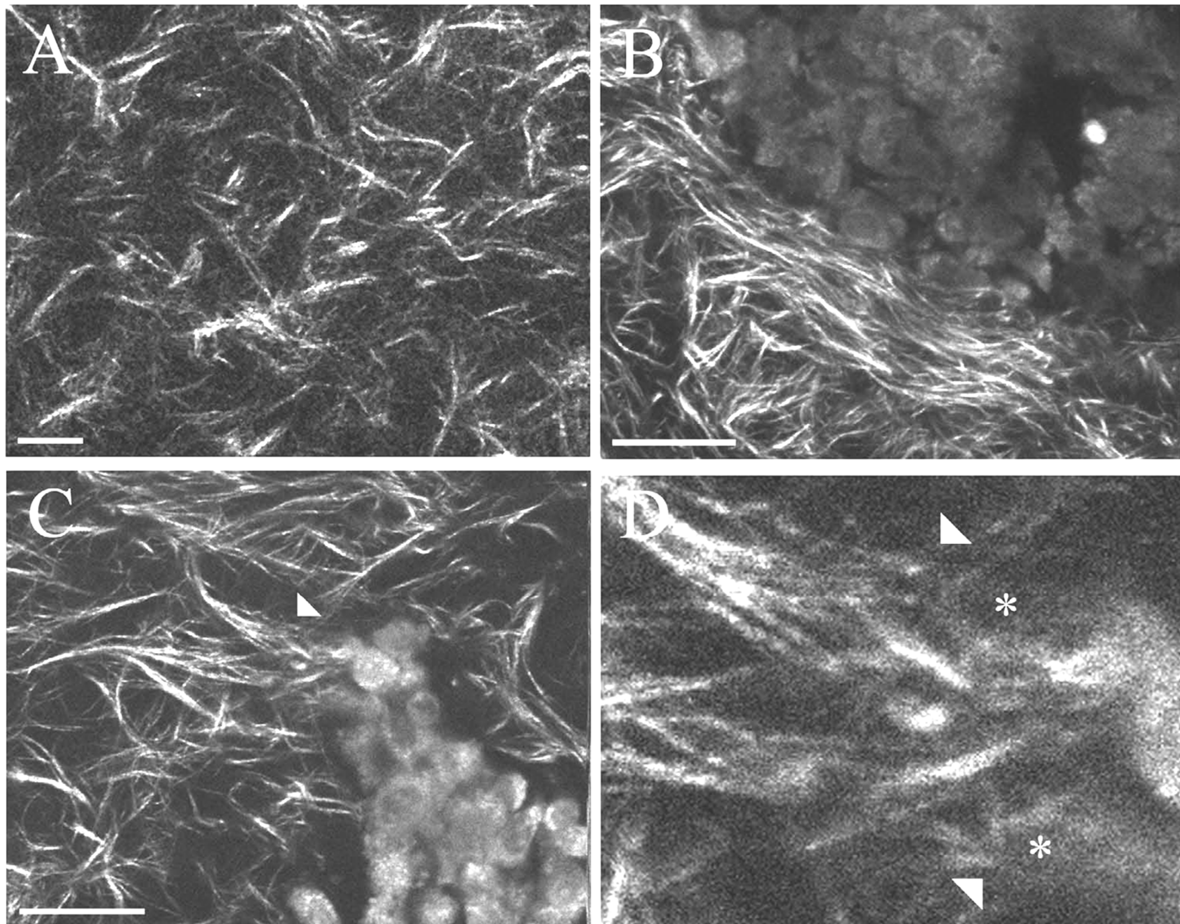


Figure 7. Collagen matrix reorganization by tumor cells facilitates local invasion of tumor cells. Combined MPE/SHG imag-ing of tumor explants cultured within 3D collagen gels for eight hours demonstrates that tumor cells reorganize a previously random matrix to facilitate invasion. (A) Region of 3D collagen gel remote from the tumor demonstrating the random orienta-tion of collagen present within 3D collagen gels in a region that has not been reorganized by a specific outside force. This ran-dom organization is specifically altered by cells from tumor explants as the cells contract and reorganize the collagen matrix. Similar to data in live intact tissues, non-invading regions show collagen pulled in near the explant but wrapped around the tumor boundary (B), while at regions of tumor cell invasion into the collagen gel, collagen has been radially aligned by the tumor cells (white arrow heads C) with cells (*) in direct contact with the collagen matrix (white arrowheads; D). Therefore, at regions of tumor cell invasion, collagen has been reorganized to a radial alignment from a random orientation, indicating a structural realignment of collagen fibers facilitates local invasion. Scale bar equals 25 μm.

Discussion

Intrinsic fluorescence detection with multiphoton excitation in combination with SHG facilitates three-dimensional, high resolution, imaging in unfixed, unsectioned, unstained mammary tissues. This imaging provides information commonly obtained with classical histology and EM without the need for complex and destructive sample preparation, and with additional structural information in four dimensions. With MPE/SHG, mammary gland tissue could be clearly imaged at depths of 440 nm, and changes in collagen density could be reliably detected. Furthermore, three-dimensional imaging of tumors in situ revealed three now defined TACS, which provide standard hallmarks to locate and characterize tumors:

TACS-1, the presence of dense collagen, indicated by increased signal intensity at a region around the tumor as a standard hallmark for locating small tumor regions; TACS-2, the presence of taut (straightened) collagen fibers stretched around the tumor, indicating growth leading to increased tumor volume; and TACS-3, the identification of radially aligned collagen fibers facilitating invasion, which may be indicative of the invasive and metastatic growth potential of a tumor. Together these signatures may serve a mechanism to help identify and characterize breast tumors in experimental animal models as well as human cancers and fresh tumor biopsies.

The breast epithelial cell-ECM interaction is responsible for influencing cell polarity, proliferation, differentiation, adhesion, and migration [44,45] and type I collagen is an important regulator of mammary ductal formation during development [4]. Analysis of normal mammary glands reveals collagen fibers wrapping around, as well as radiating away from, the duct (Figure 2A: b). This organization is remarkably consistent with the observation that in fixed whole mounts of developing mammary gland, analyzed with multiphoton microscopy, collagen fibers are "pulled in" perpendicular to the terminal end bud [46], similar to what we observe for radially aligned collagen fibers near tumors (TACS-3). Combined, these morphologies provide insight into the structure-function relationship in the mammary gland and imply that collagen may provide directional cues during development that also influence changes in the normal mammary gland. For instance, the crimped (wavy) collagen structure (i.e. Figure 2A: a,b,e,g) is consistent with numerous reports of crimped collagen fibers in connective tissue that allow normal tissue deformation with a strain-stiffening behavior [47,48]. This behavior may hold true for the mammary gland as well, allowing for tissue deformation and normal ductal growth and involution without over constraining the system, yet providing adequate levels of tensile resistance to contracting cells and resisting large deformations that can damage the tissue. The less numerous taut fibers may serve a different purpose. They may act as locally constraining structures at the single cell level and may act to interconnect various ducts in the tissue together and to the nipple structure (Figure 2A: f), which may transmit mechanical signals to the ducts during activities such as nursing to elicit mechanotransductive signaling related to lactation. Furthermore, such mechanical signals acting directly on epithelial cells or transmitting stress across the basement membrane would be amplified by increased breast tissue density. Hence, increased breast tissue density in vivo may promote carcinoma formation by increased mechanical signaling events in dense tissue, consistent with in vitro work showing that increased matrix density alters breast epithelial cell signaling [49].

The importance of matrix composition and morphology around the mammary epithelium is illustrated by studies showing that misregulated stromal-epithelial interactions can promote tumorigenesis [6-8] and the fact that breast carcinomas often exhibit desmoplasia (excessive collagen surrounding an invasive tumor [50]). Moreover, cancer cells can locally invade across basement membrane and collagenous stroma to spread into neighboring ECM environments, where they can migrate further to enter lymphatic and blood vessels, resulting in metastatic growth in distant tissues [40,51]. Therefore, understanding the mechanisms of invasion in vivo is of great importance. Yet, to our knowledge, no study has visualized local invasion in endogenous tumors in vivo in relation to stromal organization. Consequently, it is noteworthy that we observe alignment of collagen fibers, and association of individual cells with those fibers at regions of local invasion in live tissue (TACS-3), which is similar to observa-

tions of individual cell migration along collagen fibers in a xenograft model [9], and confirms and expands upon in vitro studies in 3D matrices that have identified collagen reorganization (alignment) at the front of invading cells [22,40,41]. Moreover, the concept of alignment-facilitated invasion appears to be of significance in collective cell migration (e.g. tubulogenesis in the mammary gland; [41]) as collagen alignment is noted at the terminal end bud during invasion of the mammary ductal tree [46]. Thus, collagen alignment may facilitate motility and migration during normal development, while tumor invasion may resemble misregulated developmental processes.

Conclusion

The data presented indicate that tumor cells often localize near dense collagen or promote a desmoplastic response and contract and localize collagen, followed by tumor growth and expansion (stretching) of the collagen matrix leading to matrix reorganization (possibly assisted by proteolytic cleavage [40,43] to release collagen fibers) to help facilitate local invasion. This matrix reorganization would require enhanced contractility and motility of the tumor cells, which may explain the increased presence of Rho and ROCK, in invasive cancers ([52], and references therein). Although a number of mechanisms, such as growth factor and integrin signaling and protease secretion and activity, are associated with invasion and metastasis, it seems likely that GTPase-regulated motility events are also involved these processes. Hence, the mechanisms behind local invasion may include matrix reorganization through GTPase-mediated tumor cell contractility (P.P.P. and P.J.K unpublished observations), leading to an aligned matrix that facilitates local invasion.

Competing interests

The authors declare that they have no competing interest. However, portions of the technologies presented in the manuscript are patent pending. The authors have no interest, arrangement, or affiliation that could be perceived as a conflict of interest in the context of this manuscript.

Authors' contributions

PPP conducted all MPLSM, SHG, SEM, and histology experiments, managed mouse colonies, performed 3D cell culture experiments, analyzed the imaging data, and prepared the manuscript and figures. DRI assisted with mice and performed 3D culture experiments. JMC performed TEM imaging of mouse glands. KWE and JGW assisted with specific technical aspects of nonlinear imaging and data analysis as well as project coordination. PJK participated in the design and coordination of the project and assisted with data analysis. PPP, KWE, JGW, and PJK cooperatively designed the project and discussed data interpretation and analysis. All authors participated in critical editing of the manuscript and read and approved the final manuscript.

Additional material

Additional File 1

MPM/SHG imaging of collagen and endogenous fluorescence in connec-tive tissue and reconstituted 3D matrix. (A) SHG image of type I collagen in mouse Achilles tendon. (B) MPM/SHG image of cellular endogenous fluorescence and collagen in skin. (C) Collagen and NADP(H) detection with combined MPM/SHG imaging of mouse pectoral muscle. (D) SHG imaging of type I collagen in a reconstituted three-dimensional gel.

Additional File 2

Col1a1tmJae mice possess collagen dense mammary tissue. Histology of homozygous col1a1 mice (A) showing increased collagen surrounding the mammary duct as detected with H&E, trichrome, and picrosirius red (Picro) staining. (B) Increased collagen is also

present in heterozygous col1a1 mice as detected with H&E and picrosirius red staining (PS).

Additional File 3

MPLSM examination of TACS-2 and TACS-3 in H&E sections of PyVT tumors. Left Column: Non-invading region of the tumor showing TACS-2 (see middle left panel arrows) that can be confirmed with MPLSM (bot-tom left). Right Column: Invading region of the tumor showing TACS-3 (see middle right panel arrows for examples of invading cells) that can be detected and confirmed with MPLSM (botton right). Boxes in top row indicate region examined in the middle panels.

Additional File 4

Movie file showing MPE/SHG imaging of collagen surrounding the mam-mary duct at >440 μm into the live tissue.

Additional File 5

Movie showing MPE/SHG imaging of TACS-1.

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Materials of the Conferences

HYGIENIC ANXIETY INDEX AS HEALTH LOSS RISK ESTIMATION CRITERION

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The most important component of life mode of any person is his activity. The motive foundation of human activity is his needs. At present specialists suggest various classifications of these needs. In accord with one of the most recognized concepts, the concept that was worked out decades ago by Abraham Maslow, there is a certain hierarchy of human needs (Maslow A., 2003, Ilyin Ye.P., 2002). This hierarchy is determined by the priority of this or that need in the process of motivation formation, and through them – of this or that human activity. The main difference of higher needs from those taking in the hierarchic structure the low, basic level, is the necessity of prior satisfaction of the low level needs. The dissatisfaction with them restrains or suppresses any higher, social, need and the corresponding human activity, by this depriving a human being the main sense of his existence – social essence of objective reality.

The safety need belongs to the number of basic, fundamental needs. In modern social psychology this very need is considered to be one of the main basic, vital needs.

Objectively, the term "safety need" integrates the whole group of various needs, the wish not to have a risk of health loss among them, which, in their term, are mediated with both objective (the environment state, dwelling and food provision and etc.) and subjective (the ability to evaluate this or that menace for personal security) factors. A certain meaning here is given to the urge not simply to avoid diseases or death, but the urge to secure social existence, e.g. the urge to avoid a loss because of the health, social status, material situation, professional or personal achievements, etc.

As the results of specially carried out by us research testify, among youth of different regions of Russia (Savelyev S.I. and co-authors, 2004) various needs of the young people, among them the safety need, are directly connected with social health in the widest understanding of the term "social health". In particular, to the number of medico-social manifestations of safety need dissatisfaction belongs not only the increased morbidity, but also hygienic or opposite to it deviant activity of young people, the manifestation of distress among them, etc.

It should be noted that in modern social psychology a distinct direction dedicated to human safety problems under the conditions of extreme situations was formed. This direction was named "catastrophism". On the analogy, there came into being a peculiar specific subject field – "disaster medicine". Both of the directions analyse scientific and practical problems of human safety proceeding from the possibility of emergency situations uprising or under the condition of extraordinary events having taken place. At that, as a measure of safety loss feeling in connection with some or other events, the appropriate human responses are considered – fears, i.e. extreme forms of safety loss feeling. And for a quantitative estimation of fear incidence in the mass of observations different derived quantities obtained by means of possible catastrophic events (beginning with the most probable and finishing with the most impossible - alien invasion, masons' conspiracies, etc.) fear manifestation intensity and frequency regard.

Studying the hygienic aspects of safety it seemed to us inappropriate to rely on the showings rooted in various fears because expressed fears of health loss as the constant element of standard life mode occur rarely and their long-term or continuous existence is often connected with psychic deviations (phobias, etc.) The most reasonable, as the carried by us research showed, is the use of statistical criteria developed with regard of literal and non-literal perception of various, prevalent enough hygienic risks – health loss risks which actually are "every-day" ones for modern civilization. On the basis of these risks we worked out the hygienic anxiety index (HAI). While choosing this index the experience and methodical approaches, used by social psychologists in the course of realization of Russian National part of comparative International Research "Catastrophic

consciousness in the present-day world" (Shlapentokh V.E., Shubkin V.N., Yadov V.A., 1996), were taken into consideration.

The HAI level was set in on the basis of distribution of the answers to two groups of questions. The first group of questions was formulated as follows: "Do you come across such factors of health risk loss as malnutrition, stress overload, smoking, alcohol drinking, negligent attitude to health, improper life mode, hypodynamia, and the like?" The second group of questions, touching the noted risk factors and being not different from the first group actually, was formulated in some other way: "Do you consider: improper life mode, ecological factors, inheritance, disregard to your own health, working and learning conditions, shortage of aids and appliances to be a possible cause of sickness?" Altogether, there were four HAI levels considered:

the low level of hygienic anxiety. There the respondents who considered that they don't come across hygienic risks in their every day life, belonged. The numerated risk factors were not thought by them to be real factors of menace for their health;

the weak level. The respondents believed that only single risks were possible;

the level of moderate hygienic anxiety. Everyone of the questioned admitted the existence of some risks;

the level of strong hygienic anxiety. The respondents thought that the majority of the numerated risks were an objective menace for their health.

As the results of the investigation statistical data manipulation show, among 2500 young people aged under 25, studied in different educational institutions of St.-Petersburg, Bryansk and Lipetsk Regions, the low levels of hygienic anxiety were detected in 40,6%, weak - 41,4%, moderate - 11,3%, strong - 6,7% of the cases. The essential influence on these showings' distribution was made by the incidence of stress loads among the examined young people. In the group of respondents who didn't mark psycho-social stresses or marked rare stress situations, the moderate and strong levels of HAI were marked in 12,5%. Among the respondents who marked continuous stress loads, this showing increased more than twice as much (28,7%). It should be noticed that home, "every day life" stresses and "learning" stresses were equally strongly connected with the HAI showings' distribution (X2 = 409,0, P«0,001, Cnorm = 0AL and X2 = 535,8; P«0,001 and Cnorm = 0,52).

Thus, the more psycho-social stresses prevail (irrespective of their "nature"), the higher was the level of hygienic anxiety. Considering the incidence of stresses in the context of their organic connection with adaptation processes one could expect the existence of interconnection between the HA levels, the results of psychosocial integration processes and the levels of psychosocial adaptiveness.

The statistical analysis of the collected data proved the availability of such an interconnection. So, among young people with low psychosocial adaptiveness the moderate and strong levels of HA were marked in 11,6%. In the group of high adaptiveness – almost three times as much (in 28,6%of the cases). I.e. where the processes of psychosocial integration are the most active and the highest result is reached, the levels of hygienic anxiety are higher.

It should be noticed that the organic connection of psychosocial integration processes with stress reactions' frequency is not stiff functional. In practice this interconnection can be estimated only statistically, i.e. in the form of one or another manifestation probability. It is connected with the fact that in objective reality the system "stress-adaptation" exists under the conditions of many factors' interconnection. And the more "softly" this interconnection is, the less noticeable for a young person stresses are, even if they are objectively present as natural elements of adaptation processes. And vice versa, at close interconnection of adaptation factors stresses become more noticeable.

As the result of difficult and intensive psychosocial integration, the high frequency of psychosocial stresses is often attended by low showings of psychosocial adaptiveness. So a well known to the specialists phenomenon of one or another "adaptation cost", i.e. the cost value of everything that in daily use is called "body defenses" spent on achieving adaptiveness to some or other factors, is found out (Bayevsky R.M., 1979). These expenditures can be extremely essential (adaptation high price) and lead to the most negative consequences despite achieving high adaptiveness. As a spectacular example a well known situation in the professional sport can serve, when high, and often - ultimate loads with which a trained sportsman copes well by virtue of his adaptiveness to them, almost inevitably cause severe remote effects.

Table 1.The distribution of psychosocial integration levels of the examined young people considering the stress manifestation frequency (in % from the general number of the examined)

Total stress intensity	Psychosocial adaptation level			
	high	medium	low	total
Low	14,2	10,2	4,4	28,8
Moderate	12,9	16,1	17,6	45,3
High	3,6	6,8	15,2	25,8
Total	30,7	33,1	36,2	100,0

As it is seen from the data represented (Table 1), the group of the high psychosocial integration level against the background of low stress loads, i.e. the group of low adaptation price, made 14,2% of the whole mass of the examined youth. The size of the opposite to this one group of high adaptation price (high stress and low level of adaptiveness) was practically the same - 15,2% of the examined.

Hygienic anxiety index was in close connection with the considered above adaptation price. Where the adaptation price was the highest, the index of hygienic anxiety was essentially higher. In particular, among young people from the group of high psychosocial integration the HAI reached 32,1%. In the group of moderate adaptation price it decreased up to 18,9%, and in the group of low adaptation price it didn’t exceed 9,3%.

The close interconnection between such phenomena as the level of hygienic anxiety and the character of adaptation processes allows considering the increased level of hygienic anxiety, i.e. fear for one’s health, as a defensive reaction, a natural and integral part of adaptation syndrome, the principles of which “…in general can be applied …to even whole communities of people” (Selye H., 1979).

Based on the above, one can consider that the level of hygienic anxiety or its extreme manifestation – fear, is an obligatory element of active psychosocial integration. The statement, that the correct using of the fear factor is an obligatory component of healthy lifestyle social regulation, issues from here.

And it is necessary to remember that fear is like a drug, the overdosage of which can lead to heavy consequences, and shortage – deprives it efficiency as the most important medico-social factor of healthy lifestyle.

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BLOOD SERUM ANTIOXIDANT SYSTEM AND IMMUNITY STATE AT GESTOSIS IN PLURIPARA WOMEN

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The purpose of the research is to study the role of lipids in gestosis pathogenesis and immunity state at repeated deliveries. The problem is to define blood serum antioxidant system state (AOA) and lipid peroxidation (LPO) in 25 pluripara women (PW) with gestosis and 14 PW without complications, and to study the immune status in 50 PW. Malondialdehyde increase in blood serum of PW with gestosis (18,09 ±0,071 nmol/ml at gestosis and 10,48 ± 0,54 nmol/ml in the control), hydroperoxidation inhibition degree lowering on the quick h rise (0,401±0,040 and 0,573±0,01) and oxidation enhancement of non-esterified aliphatic acids on the slow AOA h rise (0,368+0,012 and 0,476±0,029) have been detected. The quantity reduction of T- (32,4±2,5% and 364±21,9 per

mcl) and B- (13,9±1,5% and 192±8,4 per mcl) lymphocytes, moderate enhancement of their blast conversion and migration inhibition index increase (62,08±2,07% and 33,65±3,14), circulating immune complex level increase (light transmission percentage decrease up to 65,4±2,289% in PW with gestosis) have been detected. So, the activation of LPO processes, blood AOA inhibition and evident immune depression can be evaluated as the components of gestosis pathogenesis in PW. Preventive treatment was carried out for 68 PW from the gestosis risk group in terms of 20-22 and 30-32 weeks during 10-14 days. Besides the general pathology treatment the action on the peripheral circulatory dynamics was provided; antioxidant therapy (Chophytol), metabolic disorders' and immune shifts' correction was carried out. The I degree gestosis frequency reduced 2,4 times as much, II degree – 1,4 times, III degree – 1,1 times. Thus, early being registered, gestosis risk groups forming, carrying out complex preventive therapy will allow decreasing gestosis frequency and severity in PW.

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NORMOBARIC HYPOXITHERAPY AS AN IMPORTANT FACTOR OF NON-MEDICATION TREATMENT OF ARTERIAL HYPERTENSION NON-ADULTS

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Normobaric hypoxitherapy, that is breathing with an oxygen mix with a reduced content of oxygen, concerns perspective preformed physical factors which are successfully used in treatment of children and teenagers with arterial hypertension. The data for arterial hypertension prevalence among non-adults vary rather widely and make from 4,8 to 14,3 %.

On the basis of RAMS SB Clinic normobaric hypoxitherapy correction was received by 89 arterial hypertension teenagers. According to the age composition the distribution was as follows: there were 61 (68,5 %) boys, 28 (31,5 %) girls; there were 40 (44,9 %) children aged from 12 to 15, and older than 15 - 49 (55,1 %) teenagers. The findings got were compared to the ones of the control group balanced quantitatively, by sex and age with the basic one. The research was carried out on a hypoxicator "Everest-1" (Russia), МПФК.941589.001-05ПС. The course of treatment consisted of 10 daily manipulations carried out in morning hours with obligatory observance of not less than 30 min interval after meal. Breathing with hypoxic mixture was carried out by a mix in an interval mode (3:1, 5:1). We had been modified the technique of carrying out normobaric hypoxitherapy depending on the age and seance number of the children and teenagers. In the course beginning the exposition did not exceed 10 min with gradual increase up to 40 min. Further séance lasting time was inappropriate as could cause unwished vegetative reactions. Arterial tension indices were chosen to be the efficiency criteria. The following results were obtained. In the group receiving normobaric hypoxitherapy the dynamics of arterial tension indices was as follows: at the age of 12-15 the average arterial tension level was 131,9/75,2 (higher 95percentile) before the treatment, a significant arterial tension decrease up to 117,5/72,2 (corresponds to 90percentile) was registered after the treatment; in teenagers older than 15 - 133/81,1 (higher 95percentile) before the treatment, 114,9/71,9 (lower 90percentile) – after the treatment. In the control group average arterial tension index changes turned out to be less significant: they corresponded to 95percentile in children aged 12-15, and 90percentile - in teenagers older 15. More over, disappearance of concomitant complaints – cephalalgia, dizziness, asthenic implications, instable moods – conditioned by vegetative disfunction, was marked in 83,2% of the cases in the children receiving normobaric hypoxitherapy. While in the control group subjective complaint regress was registered only in 43,1% of the cases.

Thus, including normobaric hypoxitherapy in rehabilitation complex for arterial hypertension non-adults authentically decreases arterial tension

indices and promotes concomitant complaints regress, that improves life quality and social adaptation of teenagers with arterial hypertension and allows recommending the specified physical factor to application.

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ANALYSIS OF PERINATAL MORTALITY AMONG YOUNG MOTHERS

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Despite decline in the birth rate among women of reproductive age, a steady increase of pregnancies and births among very young women has been observed in Russia in recent years. Repeated studies have shown that pregnancy and birth complications occur much more often among very young women than among 20-25 year-olds, and perinatal fetus mortality among the 13-17 years old women reaches 9.1-18.7%.

The purpose of our study was to analyze the structure of perinatal fetus mortality among 13-18 years old women.

Subject matter and methods of our research were as follows. 192 cases of perinatal fetus death in very young women, who had given birth at the maternity homes №10 and №15 of the city of Saint Petersburg, Russia in the last 20 years, were retrospectively analyzed. There were 83, 35 and 56 cases of antenatal, intranatal and postnatal death of fetuses, respectively.

Results and discussion: our analysis showed that asphyxia (36.9%), intrauterine fetus infections (35.4%) and congenital abnormalities (18.8%) were the top three causes of perinatal fetus death among young women. These were followed by birth trauma (6.1%), pneumonia (2.2%) and hemolytic disease (2.0%). The frequency of asphyxia causing perinatal death was not constant: it was 45.7% in the antenatal period and 19.4% in the postnatal period. Opposite data was obtained during studies of intrauterine infection causing perinatal death of fetuses and newborns. It was the highest (53.6%) in the postnatal period. Congenital abnormalities causing fetus death were the highest (7.2%) and the lowest (3.6%) in the antenatal and postnatal periods, respectively. Intranatal birth trauma led to the death of newborns in 7.5% of cases, whereas consequences of the postnatal birth trauma – in 14.3%. Hemolytic disease caused fetus death in the antenatal period in 4.8% of cases.

Considering implications of the age issues for perinatal fetus mortality, it is necessary to point out that intrauterine infection was the number one cause of fetus death among 13-15 years old women. It remained the highest in both antenatal (4.8%) and postnatal (3.6%) periods.

Asphyxia was the main cause of the perinatal loss (21.7%) among 16-17 year-olds. At the same time, in that age group, generalized intrauterine infections (5.7%) were the main source of fetus death in the early neonatal period. The most frequently occurring cause of fetus death among 18 year-olds was also asphyxia (20.5%), however, 41.2% of death cases that took place in the first seven days after the birth were due to generalized infection.

Based on the above information, the following conclusions can be drawn. For all age groups,

it is of paramount importance to control influence of infections as it was number one cause of perinatal mortality among young women. Therefore, preventive measures against perinatal mortality among young mothers should include sanitation of infection sources.

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INFLUENCE OF CHRONIC AFFECT OF SULPHURIUMCONTAINING GAS ON A RAT THYROID GLAND.

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The problems of influence of sulphuriumcontaining gas on thyroid gland now are investigated insufficiency. Between that the urgency of the given problem is defined by the necessity of prophylaxis of pathology of a thyroid gland at the workers of manufactures connected with sulphuriumcontaining gas.

We carry out an experimental research on study of chronic influence of sulphuriumcontaining gas on a rat thyroid glands. The estimation of such influence is investigated with the help of morphometrical research of a thyroid gland on the basis of techniques G.G. Avtandilov, V.L. Bykov and O.K. Khmelnitsky [1,2,3] . The rat thyroid glands , not undergone to influence of gas (control group) are investigated also.

With the help of morphometrical rules MOB-15M have determined in a micron: D- follicles diameter, h_{Ef} – height of a thyroid epithelium. Planimetrical research was based on a determination in a % of the relative area of a vascular channel Vas, relative area of a colloid C and relative area of stroma S and E – relative area of follicles epithelium.

The results are submitted in the table. In the histologic specimen of thyroid glands of the animals which have undergone to influence of gas, the variegation of a structure of a organ is revealed: presence of sites of normal frame and areas of a destruction of gland tissue.

At experimental animals the tendency to decrease of a follicles diameter is marked, height of a thyroid epithelium decreases.

In the rat thyroid glands, undergone to influence of sulphuriumcontaining gas, reveals decrease of the relative area of and areas of vessels, at the same time significance grows the relative area of a colloid and srtoma, at the expense of an edema and thickening of connective layers.

Table 1. The results are submitted:

Parameter		Group	
		Control	Experimental
D	M ± m	61,2 ± 1,3	58,9 ± 1,2
h_{Ef}	M ± m	8,0 ± 0,2	7,8 ± 0,3
E	M ± m	52,8 ± 0,6	49,0 ± 0,7*
C	M ± m	35,2 ±0,6	38,2 ± 0,5*
Vas	M ± m	3,3 ± 0,39	2,7 ± 0,2*
S	M ± m	8,7 ± 0,5	10,1 ± 0,7*

Note: * - statistically significant differences.

At experimental animals the destruction and follicles collabiration ,exit of colloid in interfollicular space are observed.

These morphological changes at the end can result in infringement of function of thyroid gland and formation of cysts of the given organ.

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STRESS-CHANGES OF IMMUNOLOGICAL REACTANCE IN CHILDREN WITH CONGENITAL OBSTRUCTIVE UROPATHYS

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Actuality of the problem. Congenital obstructive uropathy (COU) is an extremely extended pathology in children's practice. These anomalies in a range of patients can be complicated with various conditions, but their especially frequent and early complication is secondary pyelonephritis which essentially burdens the main pathology run and creates additional troubles in the patients' treatment. It is conditioned not only by inflammatory changes in the pelvicalyceal system and tubulointerstitial tissue of a kidney, but also by the nascency of immunopathological reactions and different immune alterations.

The changes of immunological reactivity at COU undergo considerate changes depending on the degree of ureteropelvic obstruction and the potency of secondary infectious process. Other factors can influence the intensity of immune alterations, but in the literature available we haven't come up the data for how a surgical stress and anesthetic management during an operative intervention at COU in children influence different components of immune response.

Purpose of the research. The purpose is to study the immunologic reactivity changes in children with COU; to substantiate the balanced treatment policy taking into account the diagnosed immune alterations.

Problems of the research. 1) to study changes of cellular and humoral immunity values in children with COU; 2) to investigate the dynamics of cellular and humoral immunity values' change before and after the operative intervention in this group of patients; 3) to substantiate the balanced treatment policy taking into account the diagnosed immune alterations.

Materials and methods of the research. We examined 40 children (general group) from 5 to 15 years old with COU complicated with secondary chronic obstructive pyelonephritis. Among them there were 28 (70%) boys and 12 girls. The surgical organ-saving treatment was prescribed for all of them. General clinical, clinical and laboratorial, biochemical and instrumental examinations were performed for the general group. Alongside with this CD_3- and CD_{22}-lymphocyte content (PCR with homogeneous antibodies), CD_4- and CD_8-lymphocyte value in blood (method of indirect immunofluorescence with homogeneous antibodies) were detected in all the children the day before and the day after the surgery; immunoglobulin (G, A, M) levels (method of radial immunodiffusion using antichain serums) and concentration of circulating immune complexes in blood serum (precipitation method) were investigated as well. The material obtained at the immunologic reactivity parameters' investigation in the observed patients was compared to the specified indexes' investigation results in 232 children of the same age of I-II health groups living in Kirov and Kirov Region (the control group). All the patients were provided with a standard complex anesthesia service: general inhalant endotracheal anesthesia with halothane + intravenous induction of stupefacient analgesics. The Haynes-Anderson's operation was carried out for hydronephrosis patients; Cohen's operation was carried out for patients with vesicoureteral reflux; Marshall-Stevenson's operation – for obstructive ureterohydronephrosis patients.

Results. Immunologic reactivity changes in the general group of patients with COU before the influence of surgical stress and anesthesia service manifested in the authentic reduction of CD_3-lymphocytes' and CD_8-cells' relative count in blood; G and M immune serum globulins' value increase. After the surgical aid and its anesthetic management the authentic reduction of CD_3-lymphocytes' relative count, relative and absolute count of CD_4-lymphocytes and CD_8-cells, and G and M immune serum globulin increase.

Conclusions:

1. There are evident immunological status changes in children with congenital obstructive uropathy.
2. These abnormalities redouble under the influence of a surgical stress and preparations of anesthetic management.

3. The diagnosed immune alterations define the advisability of using immunotropic preparations in anesthetic management of the operations concerning children's COU.

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CLINICAL VALUE OF THE DEFINITION OF SPECTRUM UROPATHOLOGICAL AGENTS IN CHILDREN WITH OBSTRUCTIVE PYELONEPHRITIS AT THE PRESENT STAGE

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In the context of children's urinoexcretory tract obstructive disease number growth tendency and a large percentage of complications of these diseases with secondary infectious processes, we undertook an attempt to evaluate the features of pyelonephritis microflora in children with congenital obstructive uropathy COU) in its dynamics and to clear up the reasons of various potency of inflammatory processes in different patients. Patient histories of 5-14 year-old children with COU, who had been treated in the surgical department of Kirov Regional Clinical Children's Hospital from 1997 to 2002, and the data for urine culture obtained during the children's examination in three months after discharge from the hospital were subject to the retrospective analysis. Obstructive pyelonephritis complicated COU in 90,4% of the cases, 52 patients being examined.

At the admission to the hospital St.aureus (42,3%) were cultured more often, more rarely – in decreasing order- epidermal staphylococcus, collibacillus, Klebsiella, saprophytic staphylococcus, streptococcus, enterobacterium, seracia. The culture was negative in 13,7% of the patients. In the dynamics the microflora had been changing and, at the discharge of the child from the hospital, E.coli (23%) were detected more often, more rarely – epidermal staphylococcus, blue pus bacillus, mycology, aurococcus, Klebsiella, Proteus, enterobacterium. The culture was negative in 34% of the patients. In three months St.epidermidis, E.coli (по 13,5%) lead, yeast-like fungi were detected in 23,5% of the cases. Blue pus bacillus, different staphylococcal associations, Proteus, Seracia and aurococcus were cultured more rarely. The urine culture had no results in 21, 3 % of the cases.

For the quantitative concept of intoxication syndrome as one of the inflammatory process potency component we calculated the leucocytic index of intoxication (LII). In the patient general group at the admission to the hospital it was high and in average it was equal to 3,42. In the dynamics normalization of the index was marked. Significant differences of the LII meanings were detected in "aseptic" diseases (0,98) and COU with pyelonephritis (3,6). More than that, we paid attention to the fact that the LII at the admission was much more higher than overall average (≈6,93) in a particular group of patients. The disease forms of these children were very different, and all of them were complicated with pyelonephritis. Having compared the data we found out that E.coli. was cultured from the urine in 75% of the cases during the first term of the research in a group of patients with the most active pyelonephritis.

By virtue of our research results we can make the following conclusions:

1. The status severity of sick children with COU is primarily conditioned by the activity of secondary infectious process, and the laws of representation in microbiological spectrum have stage character.
2. The maximal evidence of the intoxication syndrome is typical of coli-mediated secondary chronic obstructive pyelonephritis.

3. As fungi and Proteus had never been cultured at the children's admission to the hospital, their identification should be evaluated as a complication of antibacterial therapy at the discharge from the hospital and in long-term period.

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DYNAMICS OF ELECTROENCEPHALOGRAPHIC INDICES OF THE COGNITIVE PATHOLOGY AT SCHIZOPHRENICS WITH PAROXYSMAL AND CONTINUOUS CLINIC COURSE UNDER THE INFLUENCE OF PHYCHOPHARMACOTHERAPY.

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Schizophrenia is one of the most important problems both for modern clinical psychiatry, and for the science dealing with human brain in whole. According to specialists´ estimate, approximately 1% of all population in industrially developed countries are subjected to this disease (Sedok B., Caplan G.I., 2002).

Schizophrenia is heterogeneous mental disorder with wide range of disturbances in cognitive processes. The investigation of bioelectrical activity of brain could ease the objectification of these difficult and varied disturbances and prediction for a therapeutic response.

The aim of this work was the investigation of cerebral rhythms (theta, alpha and beta) according to the indices of size, topography, asymmetry and synchronization in every frequency range in order to identify the relationship between rhythms and their synchronization in space-hold and in a cognitive load. And also the development of differentiated statements for psycho pharmacotherapy of schizophrenics adjusted for indices of clinical estimate of their states and electroencephalographic parameters´ dynamics.

Materials and methods: EEG-investigation of 148 paranoid schizophrenia patients, receiving antipsychotic therapy in the condition of in-patient facility was carried out. Psychotic manifestations were qualified in 75 patients (1 group) within the paroxysmal schizophrenia on MCB-10, 73 patients (2 group) had ceaseless character of clinic course.

71 patients (main group), of which 38 (53,5%) were women and 33 (46,5%) men, had got atypical neuroleptics (risperidone, quetiapine, olanzapine), and 77 (control group)- 37 (48,05%) were women and 40 (51,95%) men got haloperidol. All preparations were prescribed in the form of monotherapy in an adequate therapeutics dosages, in some cases clozapin was connected in order to rapid relief of marked dissomny disturbances. 38 mentally healthy probationers composed the control group. All probationers were right handed. EEG mapping was carried out in case of getting to the in-patient facility in 7 days after repealing preparations with the help of electroencephalography «MICHAR - EEG - 2000». The results of investigations of spectrum capacity on ranges of theta, alpha and beta, averaged according to groups of probationers for recording in a background and in carrying out of cognitive test (calculation according to Crepelin), and also analysis of coefficient index of interhemispheric asymmetry were used in the work (KA).

Results of carried out investigations and conclusions: All EEG rhythms are symmetric and synchronic both on phase, and on frequency in a normal position against the background. In schizophrenia expressed asymmetry of cerebral rhythms and decreasing of synchronization level in comparison with norm are marked. In patients with paroxysmal clinic course, the asymmetry and lack of coincidence of EEG vibrations by phase and frequency are the most expressed, that testifies about «break» of interactions of grey matters, functional disorganization of cerebral processes and the possibility of psychopharmacological correction.

There is a complex picture of interhemispheric asymmetry in the patients with chronic clinical course, expressed for each EEG rhythm in different way. And also sharp reduction of capacity of all EEG rhythms corresponds to steady pathological condition and

difficulties of treatment in comparison with two other groups of probationers.

On analyzing the topography of spectrum capacity, the distinctive peculiarity of EEG dynamic under the influence of haloperidol was the normalization of zonal differences due to increasing of alpha-rhythm, mainly in occipital spheres. During all period of therapy, the amplification slowly-wavel spectrum with an accent in forehead spheres was noted. Atypical antipsychotics were also provoked the normalization of regional peculiarities of EEG in amplification of alpha-range, but without distinctive dynamics or with decreasing theta-rhythm.

The preparations of this group have some differences from haloperidol, and also slightly differ between themselves both according to beginning of therapeutic effects, and according to topic and dynamic of neurophysiologic indices. The received data should efficiently be applied in choosing of the method of treatment, planning of therapeutic tactics, in solving of prediction questions and forecast of psychopharmacotherapical effectiveness.

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Table 1. LF value in blood serum (ng/ml) in patients older than 60 with different bronchopulmonary pathology in comparisons:

Disease		Persons older than 60		Persons younger than 60	
		n	Average concentration of lactoferrin (ng/ml) in blood serum (M ± m)	n	Average concentration of lactoferrin (ng/ml) in blood serum (M ± m)
Community-acquired pneumonia		46	1597,1 ± 121,4 $p_5<0,01$ $p_7<0,01$	32	2566,4 ± 208,2 $p<0,01$ $p_1<0,01$ $p_2<0,01$
COPD	COPD	39	1107,6 ± 37,7 $p_4<0,05$ $p_7<0,01$	29	1479,9 ± 22,1 $p<0,01$ $p_3<0,01$
COPD	Infective bronchial asthma	35	1006,9 ± 32,8 $p_4<0,05$ $p_6<0,05$ $p_7<0,01$	21	1345,4 ± 20,6 $p<0,05$
Carcinoma of lung		35	1021,3 ± 74,2 $p_4<0,05$ $p_7<0,01$	20	1655,4 ± 65,3 $p<0,01$ $p_1<0,02$
Practically healthy persons		22	1878,5 ± 301,2	30	1176,0 ± 67,9

p – relative to practically healthy people under 60; p_1 – relative to young people with COPD; p_2 – relative to young people with carcinoma of lung; p_3 – relative to young people with infective bronchial asthma; p_4 – relative to practically healthy people older than 60; p_5 – relative to elderly patients with COPD and carcinoma of lung; p_6 – relative to elderly patients with COPD; p_7 – relative to young patients with correspondent nosologic form of the disease.

Table 2. Correlation relationships between LF levels in blood serum and immunogram showings at bronchopulmonary pathology in the elderly:

Correlation relationships	CAP	COPD	N(I)BA	CL
r_{lf}- leucocytes (abs)	↑↑ $p<0,01$	↑ $p<0,01$	↑↑ $p<0,01$	↑↑ $p<0,01$
r_{lf} – lymphocytes (%)	↑ $p<0,01$	0	↑ $p<0,01$	↑ $p<0,01$
r_{lf} – lymphocytes (abs)	↑↑ $p<0,01$	↑ $p>0,05$	↑↑ $p<0,01$	↑↑ $p<0,01$
r_{lf} - T-lymphocytes (%)	↑ $p<0,01$	0	↑ $p<0,01$	↑ $p<0,01$
r_{lf} - T-lymphocytes (abs)	↑↑ $p<0,01$	↑ $p>0,05$	↑↑ $p<0,01$	↑↑ $p<0,01$
r_{lf} - T-helpers (%)	↑↑ $p<0,01$	↑ $p>0,05$	↑↑ $p<0,01$	↑↑ $p<0,01$
r_{lf} - T-suppressors (%)	↑ $p>0,05$	0	↑ $p>0,05$	↑ $p>0,05$
r_{lf}- B-lymphocytes (%)	↑ $p>0,05$	↑ $p>0,05$	↑ $p>0,05$	↑ $p>0,05$
r_{lf}- B-lymphocytes (abs)	0	0	0	0
r_{lf} - Ig G (мг %)	↓ $p>0,05$	0	0	↑ $p>0,05$
r_{lf} - Ig A (мг %)	↑ $p>0,05$	0	0	↓ $p>0,05$
r_{lf}- Ig M (мг %)	↑ $p>0,05$	↑ $p>0,05$	↓ $p>0,05$	↑ $p>0,05$

r – correlation relationship, lf – lactoferrin, 0 – lack of correlation relationship
↑ - positive correlation relationship, ↓ - negative correlation relationship
↑, ↓ - $r < 0,5$ (weak), ↑↑, ↓↓ - $r = 0,5 - 0,7$ (moderate)

Shot report

YOUTH PERCEPTION ESTIMATION OF HEALTH LOSS RISKS AS METHODOLOGICAL PROBLEM OF PREVENTIVE MEDICINE

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The urge to risk safety as well as a kin to it feeling of danger, is a necessary condition of maturation of hygienic (conservative) forms of an individual's activity irrespective to age, and also separate social groups' activity. This statement is of great importance for the youth because the society life quality as a whole both at present and in the future depends on the adequacy of health loss or death risks perception in the youth medium.

The level of perception of one and the same objective danger can differ. The most optimal one seems to be such a level of risks feeling which guarantees self-control, prudence and foresight, that, however, corresponds more to a mature than young age. It goes without saying, that a supernormal risk feeling is not the best ground for normal hygienic activity formation. Never the less, such risk perception level is also able to influence healthy life mode development positively despite different tragically radical behaviour patterns induction danger.

The integrated research carried out by us in different domains of modern Russia and near-abroad countries is indicative of the fact that the most unacceptable one from all points of view is an undervalued or total absence of real danger perception.

Theoretical apprehension by hygienists of the safety (or danger) perception degree value, as well as the analysis on the same ground of those alterations and shifts which take place in hygienic needs formation, and, as a result, - in the formation of hygienic activity of Russian youth, remains unsolved and, in many cases, misunderstood problem. To our opinion, its scientific solution is an urgent backbone component of medico-social direction of preventive medicine.

The study of the degree of perception of some or other objectively existing of health loss risks in various social groups can be solved by means of calculating various integral estimates (on the analogy with the applied in social psychology "fear indices"). Obtaining this sort of hygienic fear indices is of great importance for clearing up such an essential feature of public health of separate youth groups as the potential of hygienic activity.

The results of hygienic fears index measuring for different groups of young people can be matched with these groups' public health showings, with the incidence of various forms of deviant behaviour in them, with the environmental pollution and other features of a specified domain state. Undoubtedly, it will give the opportunity to discuss the place of such an index of hygienic risks perception among other showings of youth state in the level of various social, professional, demographical and other groups from now forth. Such an index can serve as the criterion of a certain "general tonus" of the public health of youth, its orientation, aiming at objective dangers. As a matter of principle it can be thought of as an integral public criterion of social integration of young people, the capability to get through the problems which they face in their life. On the ground of the given approach one might compose "crisis maps" of the domains recording the land areas of increased medico-social risk degree.

The carried out by us research show that literal perception of hygienic significant risks often is more important than anything else, because it testifies to the state of young people's capabilities to solve permanently appearing problems of social growth, to keep and strengthen their health. Or to incapability of young people to solve these problems with allowable to the society methods and respectively to degrade. The features of this ability, one of the showings of which must be the index of hygienic fears, can be not less important than recording the physical, purely biological state of the youth's health.

The scientific sense of the hygienic fears problem investigation is deeply intertwined with the described in the last years by social psychologists problem of “catastrophism”, which is one of the foundational modern problems of social life.

Very different fears and the ability to apperceive various risks adequately or inadequately were and will always be a powerful social regulator. It is a weapon not only in the fight for the Nation’s health, but also a weapon of political and ideological struggle.

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INCIDENCE OF PSYCHOEMOTIONAL STRESS IN YOUTH MEDIUM

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One of the most significant parts in many ways determining the whole life mode of the learning youth is their being provided with proper accommodation. It is connected with the fact that dwelling is one of the basic hygienic demands, dissatisfaction with which is a destabilizing many human life activity sides factor. And vice versa, satisfaction of this demand benefits the lifestyle. The research results testify it: stressful situation frequency decreased noticeably with the increase of young people’s satisfaction with their living conditions. For example, among those who were fully satisfied with their accommodation the low stress frequency group made 36,5%. Among persons, who were not satisfied with their accommodation or were satisfied only partially, this group made 23,8%-22,3%. Accordingly, the high stress frequency group grew from 3,0% to 13,4%. *(x^2 = 96,2 with $P << 0{,}001$, C_{norm} = 0,23)*

The stress frequency alteration with accommodation satisfaction change depended greatly on sex and age of the examined. In particular, among persons of male gender the contingence of accommodation satisfaction and stress manifestation frequency was higher than among female one (for men *C_{norm}=0,28, for women C_{norm}=0,20 with $P<<0{,}001$).* So, among fully satisfied with their living conditions men the low stress frequency group made 49,2%. Among women with the same everyday life satisfaction this group made only 27,4%. Among unsatisfied or partially satisfied with their accommodation men there turned out to be 27,8% of persons with such stress manifestation, among women - 19,7%.

In the junior age group of learners the contingence of accommodation satisfaction and stress manifestation frequency was notably higher than in the senior age cohort (for learners aged from 16 to 19 *C_{norm}=0,25 , at the age of* 20 and older *C_{norm}=0,20 with $P<<0{,}001$).* Among fully satisfied with their living conditions respondents aged from 16 to 19 the group of low stress frequency made 40,0%, from 20 and older - 27,5%.

Among persons unsatisfied with their accommodation or satisfied with them only partially, whose age didn’t exceed 19, the given marker was 20,4%, at the age of 20 and older - 23,8%.

The objectivity of the revealed tendency was proved by the contingence of home stress incidence markers and private hygienic dwelling features (housing type and living space) as well. For example, the better was the housing type, the lower was stress frequency. If among the persons who lived in a hostel the low stress frequency group made 22,2%, among those who roomed in a multifamily unit - 28,9%, then in the group of learners who lived in a separate apartment or a private house - 31,2%. The group of high stress frequency altered accordingly. Among those who lived in a hostel this group made 7,7%, in a separate apartment or private house - 4,0% - 5,0%.

Especially vividly the specified tendency was observed at the analysis of such hygienic dwelling feature as living space. The better a family was provided with living space, the lower was stress frequency. So, among persons, who lived in the conditions when there were not more

than 6м^2 per a family member, the group of low stress frequency made 19,7%; among those who lived on the area of 6-9м^2 - 25,8%; on the area of 12m and over - 32,0%. The group of high stress frequency altered accordingly. Among those who lived in the conditions when there were not more than 6м^2 per a family member, the group of high stress frequency made 10,4%, among those who lived on the area of 6-9м^2 - 6,3%, on the area of 12m and over - 2,7%.

Interconnection of stress incidence and separate, private dwelling features as well as general satisfaction with living conditions depended on age-sex peculiarities of young people.

Among men who lived in a hostel the group of low stress frequency made 29,7%, women - 18,4%. In the group of men who lived in a separate apartment or private house this group made 39,0%; in the group of women - 30,5%. Among men who lived on the area of 6м^2 and less per a person the group of low stress frequency made 27,2%, on the area of 6-8 м^2 - 31,4%, on the area of 12 м^2 and over - 41,3%. Among women these markers made accordingly 16,1%, 22,3%o, 22,5%. The data given authentically testify that the absolute gain of markers among persons of male gender was almost three times as much than among female one; i.e. men appeared to be more sensitive to hygienic dwelling features, especially to density of occupation of the dwelling, than women.

The detailed consideration of the influence of living conditions on stress frequency separately – on schooling and housing place allowed stating the following: the more satisfied with their accommodation the young people were, the less home stress situations appeared. For example, among the learners who were fully satisfied with their living conditions home stresses were marked as “often” and “always” in 14,8% of the cases; among those who were satisfied with their living conditions only partially – in 18,4% of the cases; and among the examined people who were not satisfied with their living conditions at all these stresses were marked in every third person (32,4%).

By the way, the men connected home stress situations’ frequency with their living conditions satisfaction more actively than the women (for men C_{norm} = *0,27, for women* C_{norm}= *0,18* при P<0,01).At the analysis of the age factor role a more close connection between the accommodation satisfaction and stress situations’ frequency among younger people, than among persons of the senior age group (for the age cohort of 16-19 C_{norm}= *0,27, for the group of* 20 and older C_{norm} = 0,17 with P<0,01).

At the analysis of the role of such components of dwelling satisfaction as housing type and living space in “home” stress situations frequency alteration there were no essential age-sex differences found out.

ESTIMATION OF IMMUNOLOGIC REACTIVITY IN ELDERLY PATIENTS WITH DIFFERENT BRONCHOPULMONARY PATHOLOGY

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A method of estimation of immunologic reactivity of elderly patients with different bronchopulmonary pathology is offered. It is based on lactoferrin (LF) value definition in serum by means of enzyme immunodetection (EID) using a commercial test-system of “Vector-Best-Europe” CJSC according to the instruction attached. The results are represented in Table 1. The analysis of LF serum indicants in young and elderly patients depending on nosologic form of the disease revealed authentically ($p < 0,01$) lower albumin concentration showings in blood serum at all the cases of pulmonary pathologies in patients older than 60 (Table 1). Authentically ($p < 0,01$) higher concentration of serum LF in patients older than 60 among the examined groups was recorded at community-acquired pneumonia – CAP (1597,1 ± 121,4), and authentically ($p < 0,05$) lower showings are marked at non-allergic (infective) form of bronchial asthma – N(I)BA (1006,9 ± 32,8) and carcinoma of lung – CL (1021,3 ± 74,2).

Studying lactoferrinemia in elderly patients with different bronchopulmonary pathology we carried out a correlation analysis of LF concentration in blood serum and basic showings of immunogram (Table 2). As it is seen from Table 2, positive correlation relationships of different efficacy between the blood serum LF

content and concentration of leucocytes in peripheral blood: at CAP (r=0,53, p<0,01), COPD (r=0,34, p<0,01), N(I)BA (r=0,56, p<0,01) and CL (r=0,62, p<0,01).

Between the values of serum LF and the showings of absolute count of lymphocytes and T-lymphocytes positive correlation relationships of moderate efficacy are obtained: at CAP (r=0,57, r=0,55 accordingly, p<0,01), N(I)BA (r=0,54, r=0,51 accordingly, p<0,01), CL (r=0,62,r=0,57 accordingly, p<0,01). The same tendencies in correlation relationships are marked between the contents of LF in the serum and the showings of relative count of T-helpers: at CAP (r=0,54, p<0,01), N(I)BA (r=0,58, p<0,01), CL (r=0,60, p<0,01). These results show that at low values of serum LF the showings of absolute count of lymphocytes and T-lymphocytes, relative count of T-helpers in elderly CAP, N(I)BA and CL patients were low as well. The values of LF in blood serum had weak multidirected and unauthentic (p>0,05) correlation relationship or its absence between the other showings of the immunogram at CAP, COPD and CL. The findings allow considering that low values of LF content in blood serum immediately reflect lack of T-cell component of immune system in elderly CAP, N(I)BA and CL patients.

The results got allow recommending studying LF in blood serum as an additional test for immunologic reactivity of elderly patients with different bronchopulmonary pathology, that will widen possibilities of diagnostics. It is especially important for adequate treatment administration (including immunocorrectors) for elderly patients.

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MORPHOQUANTITATIVE INDICANTS OF SPINAL CORD MOTOR NEURON SYNAPTIC APPARATUS CHANGES WHEN EXPOSED TO X-RAY RADIATION (EXPERIMENTAL STUDY)

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The analysis of change dynamics of morphoquantitative indicants reflecting the degree of responsive and destructive changes of anterior horns' motor neuron synapses of experimental animals (guinea-pigs) over a period of 60 days after finishing single general X-ray radiation effect (dosage – 5 Gy).

A significant part of the population of all countries in the world is exposed to X-ray effect when being diagnosed or taking remedial measures in medical and prophylactic institutions during the life (Filyushkin I.V., 1998; Oghiso Y., Yamada Y., 2003). In this respect there is a necessity to study the dynamics of cinerea motor neuron changes in different parts of spinal cord (cervical, thoracic, and lumbar) when exposed to X-rays. That conditioned the demand of carrying out our research.

The research was carried out on 81 multicolored mature guinea-pig males weighing 400-450 g, from which 51 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). The guinea-pigs were exposed to single general irradiation (dosage – 5 Gy, 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 taking into account daily and seasonal radiosensibility (Shcherbova Ye.N., 1984). 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. 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 spinal’s fragments were taken from different parts of spinal cord (cervical, thoracic, and lumbar). For submicroscopy the cord portions 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. Anterior horns’ motor neurons were subject to study. Motor neurons differed from neurocytes of posterior horns in larger sizes and were represented by cells of two types - "dark" and "light". On the part of neurocytes the following morphoquantitative indicants were investigated – the general synapse density and the quantity of responsively and destructively changed synapses. Active zones’ number and their osmophility increase and thickening of postsynaptic membranes served in particular as the criteria of responsively changed synapses. The synapses changed on the "light" type (quantity reduction and variability in size of the synaptic vesicles, shortening of synaptic ribbons) and on the "dark" type (electron-density of the presynaptic parts, destruction of the vesicles, accumulation of microgranular matrix and chondrisomes’ destruction) were considered to be degenerative. (Logvinov S.V., 1998). All the findings of the morphoquantitative research were treated according the rules of parametric statistics. Hematological control (total count of erythrocytes and leucocytes) was carried out during the experiment.

Changes from the part of the synaptic apparatus of anterior horns’ motor neurons of the guinea-pigs have been marked on the 1st day after finishing the effect already, the reaction inequivalence of the specified structures occurring at the level of different parts of spinal cord. So, in particular, in 6 hours after the irradiation the showings of the total synapse quantity and those of the responsively changed anterior horns’ motor neurons’ synapses are reduced relative to the control in the majority of the parts making in cervical spine - 93,8% and 96,0%, thoracic – 95,6% and 107,0%, lumbar – 90,4% and 97,6%, accordingly ($p<0,05$). At the same time the quantity of degenerate changed motor neurons’ synapses in anterior horns, on the date indicated, exceeded the original one making in cervical spine - 137,9%, thoracic – 192,5%, lumbar – 117,4% ($p<0,05$). On the 1st day the earlier marked tendency to matching low values of total synapse density and the quantity of responsively changed synapses and high values of degenerative changed motor neurons of the guinea-pigs’ spinal cord kept retaining. It is also necessary to notice that for the responsively changed anterior horns’ motor neurons’ synapses of thoracic spine the most evident hyperosmophility of presynaptic parts is definitive. On the 5th day after finishing the X-ray effect a significant number of neurons with degenerative changed synapses with destruction focus in postsynaptic parts in anterior horns of thoracic spine attracts attention. And from the part of the degenerative changed synapses of the structures specified in lumbar spine the full-blown hyperosmophility of presynaptic parts, in which destruction foci occurred. The quantity of degenerative changed anterior horns’ motor neurons’ synapses was mostly increased in thoracic spine, where it made 238,8%, and at the same time it made in cervical spine - 134,5% and in lumbar spine - 131,2% from the original one ($p< 0,05$). Moreover, on the 5th day after finishing the irradiation effect, the showings of synapse general density and quantity of responsively changed motor neurons’ synapses were higher than the original ones only in the specified structures of thoracic part – 1,02 and 1,05 times as much accordingly, and in cervical and lumbar parts – lower than the original ones ($p<0,05$). On the 10th day after finishing the effect, at the height of X-ray sickness, from the part of some axonal terminals swelling events and “light” type changes occurred. It manifested in the fact that a few number of vesicles forming

small clusters, and sometimes their total absence, became apparent in presynaptic terminals; cases of their agglutination being also frequent. In different neuropil regions cases of synapse active zones' protraction and synaptic cleft distention up to 50-70 nm were also marked sometimes. At the same time the availability of separate terminals, where the "dark" type reaction takes place, can't help being noticed. The terminals specified have a high electron-optical density and a great number of synaptic vesicles. Compared to the previous follow-up period, increase of total synapse density values and that of degenerate changed synapse quantity making in cervical spine - 106,1% and 194,0%, thoracic one - 115,7% and 322,8%, lumbar one - 104,8% and 171,0% from the original values, accordingly ($p<0,05$) happens from the part of anterior horns' motor neurons on the 10th day. Alongside with this, responsively changed synapses' motor neurons' value showings keep on decreasing, compared to the previous follow-up periods, making in cervical spine 79,7%, thoracic spine - 89,4%, lumbar spine - 77,1% from the original ones ($p<0,05$). On the 25th day after finishing the effect the beginning of reparative processes' development is marked, that manifests in the ultrasonic level particularly in the fact that in cytoplasm of a considerable part of both "light" and "dark" motor neurons the number of endoplasmic reticulum and Golgi complex cisterns, and also ribosomes, chondriosomes, and lysosomes increases. The specified structures are revealed preferentially in perinuclear zones of a neuron. Compared to the previous follow-up period, on the 25th day after finishing X-ray radiation a combination is noted in anterior horns of all parts of the spinal cord: degenerate changed synapse number decrease and responsively changed motor neurons' synapse number appreciable increase, making in cervical spine - 148,3% and 107,1%, in thoracic one - 288,6% and 122,5%, in lumbar one - 128,3% и 107,3% from the original values accordingly ($p<0,05$). For anterior horns' motor neurons' responsively changed synapses in the specified term the increased osmophility of active zones and also full-blown node of postsynaptic membrane were typical. By the end of the observation period (the 60th day after finishing X-ray radiation), unlike the previous follow-up periods, values both of responsively changed synapse quantity and total motor neuron synapse density exceed the original ones in all parts of spinal cord, making in cervical part - 114,6% and 103,9%, thoracic - 139,9% and 115,1%, lumbar - 111,9% and 101,3%, accordingly ($p<0,05$). Responsively changed synapses of anterior horns' motor neurons of all localization parts were characterized with increased active zones' osmophility and full-blown node of postsynaptic membrane. On the 60th day after X-ray radiation the quantity indexes of degenerate changed synapses of motor neurons of the specified structures are significantly higher than the original ones in all parts of spinal cord, especially thoracic one, where it exceeds the original 2,5 times as much, while in cervical part – 1,3 times, lumbar – 1,2 times as much ($p<0,05$).

Thus, the results of the carried out research demonstrate the fact that at X-ray effect during the whole experiment (60 days) changes of morphoquantitative indicants of responsive and degenerate changes of motor neurons' synapses of spinal cord of guinea-pigs are observed; they reaching maximal manifestation degree from the part of the specified structures in cervical spine.

ULTRASTRUCTURAL CHANGES OF EPITHELIAL CELLS OF SKIN EPIDERMIS AT MICROWAVES EXPOSURE (EXPERIMENTAL STUDY)

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The analysis of the dynamics of ultrastructural changes reflecting the degree of responsive and destructive changes of skin epidermis basal layer epidermal cells of guinea-pigs during 60 days after finishing microwaves exposure (length of wave - 12,6 cm, frequency – 2375 MHz, power flow density (PFD) – 60 mW/cm2, exposure time – 10 min) has been carried out in the research.

With the development of science and technology in everyday life and industry as well as while taking diagnostic remedial measures, sources of SHF radiation (microwaves) get more and more popularity. (Gosalves J. et al., 2002; Dasdag S. et al., 2003; Yao K. et al., 2004). The first organ to be exposed to microwaves is skin that caused the necessity to study the dynamics of ultrastructural changes in epidermal skin cells,

and in particular, basaliocytes from different localization areas (head (cheek), back, stomach), while being affected with microwaves.

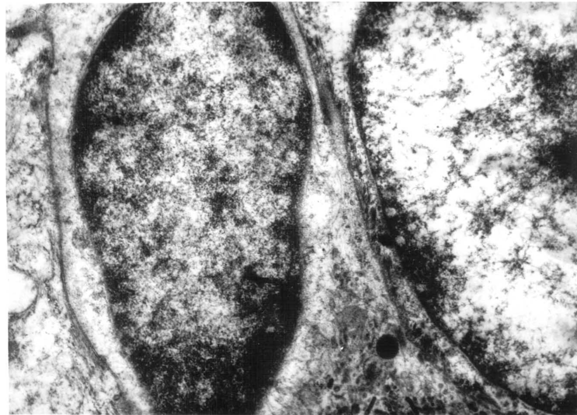
The research was carried out on 65 mature guinea-pig males weighing 400-450 g, from which 35 were used in the experiment, and 30 served as the control. Maintenance and work with the experimental animals were carried out in accordance with the rules accepted by the European Convention about the defense of vertebrate animals used for experimental and other scientific purposes (Strassburg, 1986). The experimental animals were exposed to the effect of microwaves (length of wave - 12,6 cm, frequency – 2375 MHz, power flow density (PFD) – 60 mW/cm2, exposure time – 10 min). The continuously-operated therapeutic apparatus "Luch-58" served as a microwave generator. At the irradiation a continuously-operated cylinder-shaped radiant №1 with the diameter 90 mm was used. The dosimetry was made by a thermistor bridge M3-10 with thermistor coaxid head M 5-17. After finishing microwave exposure rectal temperature of the experimental animals was measured by means of the medical electro-thermometer TPMEM-1. The irradiation took place at one and the same time of the day – from 10 to 11 o'clock in autumn-winter period taking into account daily and seasonal radiosensibility (Shcherbova Ye.N., 1984). 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. 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 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. Hematological control (total count of erythrocytes and leucocytes) was carried out during the experiment.

Right after finishing the microwave effect on the part of the guinea-pigs' behaviour some lethargy was marked, rectal temperature increased on average by 0,9-1,1ºC. During the following three days liquid intake decrease was marked. At skin section submicroscopy right after the microwave exposure in the cytoplasm of separate basal layer epidermal cells of head (cheek) and stomach skin vacuolation regions are marked. In 6 hours after the SHF radiation effect in part of basal layer epidermal cells of all localization areas, especially in head (cheek) skin, swelling of nuclei and karyoplasm depression, cytoplasm vacuolation. On the 1st day after the microwave effect, at submicroscopic research, changes of basal layer epitheliocytes are similar to the ones described in the previous term; at the same time full-blown events of perinuclear vacuolation of cytoplasm in some part of basal epidermal cells of head (cheek) skin attract great attention (Picture 2). On the 5th day after the SHF-wave effect in basal epidermal cells significant changes are revealed. Some part of the epidermal basal layer epitheliocytes of all skin areas are expanded, with vague boundaries. In the specified cells changes of nuclei which are characterized with chromatin beads relocation to karyolemma occurs. Sometimes in the specified epitheliocytes, especially in head (cheek) and stomach skin, destructive changes declaring themselves, in particular, as lysis, rhexis and pyknosis of nuclei, that undoubtedly testifies the death process of the part of the cells. Vacuolation events reach a considerable degree of manifestation in basaliocyte cytoplasm; sizes of separate vacuoles matching those of the pyknotic, sharply decreased in size, nucleus in some part of head (cheek) and stomach skin (pic. 2). In the specified time the impoverishment of both erythrocytes – up to 80,4% ($p<0,05$) and leucocytes – up to 61,7% ($p<0,01$) in peripheral blood from the control level took place. On the 10th day after the microwave exposure the changes in basal layer epidermal cells described in the previous follow-up period, though expressed in a less degree, retain. In separate epitheliocytes of stomach and head (cheek) skin the events of lysis, rhexis, pyknosis and also frank cytoplasm vacuolation events occur. On the 25th day after finishing SHF-waves exposure of thermogenic intensity a homogenious character of chromatin distribution over the nuclei of the majority of all localization areas' basal layer epidermal cells, and often - relocation of the hyperchromatic nucleolus to karyolemma, - become apparent. As an exception, in the stomach and head (cheek) skin epidermis

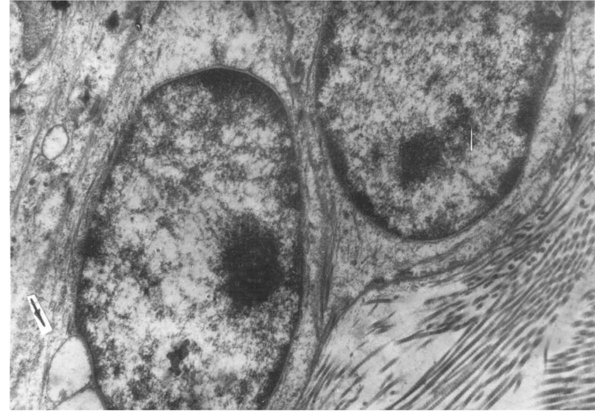
separate cells of basal layer with rhexis, lysis and pyknosis of nuclei and also cytoplasm vacuolation events are marked. On the 60th day after the SHF exposure the morphological picture on the part of basal layer epidermal cells of all localization areas differs very little from that of the control. As an exception, in single basal layer epidermal cells of head (cheek) skin cytoplasmic vacuoles occur.

The findings obtained in the experiment testify significant ultrastructural changes of basal epidermal cells of guinea-pigs' skin at microwave exposure of thermogenic intensity; the changes reaching the highest degree of manifestation in head (cheek) and stomach skin. The specified ultrasructural changes of basal epidermal skin cells, and those of destructive character as well, reach their maximum on the 5th day after finishing the microwave effect.

Picture 1. The ultrastructure of a guinea-pig's head skin epidermis basaliocytes. The control. Enlarged by 19000.



Picture 2. The event of the guinea-pig head skin epidermis basaliocyte cytoplasm vacuolation on the 1st day after the microwave effect (arrow). Enlarged by 19000.



THE PRESENT CONDITION AND PROSPECTS OF OIL SECTOR IN THE WORLD FUEL AND ENERGY COMPLEX

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The article gives the statistics of oil as one of the basic natural mineral resources. It is considered the situation with stocks of oil in regions and countries, the dynamics of its extraction, consumption, export, import, average year prices and the present state of the oil refining branch. It is also analyzed the prospects of world oil sector and the petroleum-refining industry in the near future years.

In March, 2006 OPEC promulgated "Long-term strategy" for forthcoming years. The strategy recognizes that the basic energy source in the world is oil and so it will remain.

According to the US Geological Management predicted resources of oil on the Earth are estimated as more than 400 billions tons [1]. The confirmed stocks of oil in the Earth interior as estimated on 01.01.2006 come nearer to 200 billions tons (bln.t.) (Table1).

Table 1. The confirmed stocks of oil (millions tons) as estimated on 01.01.2006 [2]

Europe and Russia	Asia	Africa	America	Oceania and Australia	Total
17375,4	115316	1517,4	44108,9	513,6	192731,3

The stocks of oil are distributed among separate countries in an extremely unequal way. About two thirds of confirmed stocks of oil is located in 150 extra large objects, huge resources of oil are concentrated in the area of the Persian Gulf (64 % of official world reserves).

The leaders of oil stocks are: Saudi Arabia (36041, 3 millions tons (mln.t.), Canada (24492, 1 mln.t.), Iran (18900 mln.t.), Kuwait (14329 mln.t.), Iraq (15512 mln.t.), Russia (14920 mln.t.), Venezuela (11678, 1 mln.t.).

It is necessary to note that at the present level of oil recovery its explored stocks can provide the world for 43-45 years [1,3] while the developed countries are provided with oil for about 8 years, and at the countries of OPEC – for 81 years. [4]. The proved world reserves of oil are constantly increasing. In 1983 they were estimated at 723 billions barrels, in 1993 – at 1023, 6 billions barrels and in 2003 – at 1146, 7 billions barrels. During 1960-2002 the volume of stocks of oil in the world grew more than 4 times [5].

The world oil recovery is constantly growing and has reached 3, 68 billions tons by 2006 (Table 2).

Table 2. Dynamics of oil and condensate recovery (mln.t.) [2,6]

	1995	1996	1997	1998	1999	2001	2002	2003	2004	2005
Europe and Russia	619,57	627,73	630,85	628,71	643,18	672,1	700,0	714,93	751,43	746,21
Asia	1304,42	1325,52	1378,87	1421,11	1430,76	1452,64	1363,48	1468,11	1545,33	1570,65
Africa	339,21	371,32	376,01	345,2	334,46	356,27	344,93	376,23	422,3	444,26
America	830,55	860,08	882,45	889,03	846,54	858,56	856,99	877,95	897,83	898,72
Oceania and Australia	31,2	34,65	35,04	33,29	33,02	36,25	34,98	29,51	25,37	25,05
Total	3124,95	3219,31	3303,22	3317,34	3287,96	3375,82	3300,38	3466,72	3642,26	3684,89

Russia (12,75 %), Saudi Arabia (12,62 %), the USA (6,95 %), Iraq (5,28 %), China (4,9 %), Mexico (4,5 %), Venezuela (4,1 %), Norway (3,87 %), Canada (3,4 %) and the United Arab Emirates (3,3 %) have the greatest volumes of extraction.

The analysis of average year rates of oil recovery growth for 75 years demonstrates its stable decrease. So, if in period from 1930 to 1960 they made 5 %, in period from 1960 to 1990 - 3 % and in period from 1990 to 2005 - on the average 1 % [7]. For each 30-years period average year rates of oil recovery growth fall by 2-3 %.

Today oil is the dominating energy source of the world energy system and its share in total energy consumption makes about 40 % and in a number of countries it reaches 60 % [8, 9].

Oil and oil products are traditionally used as motor and boiler oven fuel and also in the chemical industry.

Table 3. Dynamics of oil consumption (mln.t.) [3, 6]

	1995	1996	1997	1998	1999	2001	2002	2003	2004	2005
Europe and Russia	863,38	855,93	864	869,4	866,3	882,15	866,48	878,35	895,9	898,1
Asia	979	1037,02	1063,12	1036,83	1016,8	1204,71	1241,27	1284,79	1363,15	1389,66
Africa	72,3	76,1	78,3	79,5	80,3	117,9	116,53	119,41	123,23	128,51
America	1091,6	1136,5	1159,7	1187,4	1204,1	1284,2	1291,88	1304,63	1350,92	1354,47
Oceania and Australia	41	41,7	43,1	43,5	44,2	45,3	45,49	46,16	46,8	47,7
Total	3047,28	3145,25	3208,22	3216,63	3211,69	3534,26	3561,65	3633,34	3780	3818,44

The greatest consumers of oil are the USA (24, 7 %), China (8, 57 %), Japan (6, 4 %), Russia (3, 4 %), Germany (3, 18 %), India (3 %), Canada (2, 6 %).

The analysis of the dynamics of world oil consumption since the 1930-s years makes it single out some phases [8]:

1. 1945-1960 - the moderate growth. For these 15 years the average daily volume of consumption increased only by 10 million barrels.

2. 1960-1075 - rapid growth. In this period the world consumption increased 4 times.

3. 1975-1990 - stabilization of oil consumption at the level 60 million barrels per day.

4. 1990-2005 – the second phase of moderate growth. The consumption is 15-18 million barrels per day.

The logical analysis of these stages in the period from 2005 to 2020 lets us expect a phase of rapid growth of oil consumption.

The discrepancy between oil location and the regions of its consumption is one of the major factors of intensive development of the world trade.

The data on export and import in the world of oil are given in Table 4.

Table 4. Dynamics of export (a) and import (b) of oil from 2001 to 2005, mln. t. [2,6]

		2001	2002	2003	2004	2005
Europe(with Russia) Asia	a	401,78	401,48	404,24	426,7	417,8
	b	714,4	711,17	717,58	717,71	560,42
Africa America	a	883,62	828	871,12	962,53	981,07
	b	713,79	740,25	733,27	784,99	786,46
Ocenia with Australia	a	257,77	254,28	302,52	349,4	381,4
	b	57,7	58,39	55,55	64,4	62,53
Europe(with Russia) Asia	a	322,69	316,03	305,65	319,52	348,56
	b	620,91	588,45	641,12	654,59	648,74
Africa America	a	23,29	20,66	17,44	17,55	16,8
	b	26,09	24,02	23,67	24,33	25,1
Ocenia with Australia	a	1889,15	1820,45	1900,97	2075,7	2145,63
	b	2132,89	2122,28	2171,19	2246,02	2083,25

The greatest volumes of oil export are characteristic for Saudi Arabia (16, 3 %), Russia (11, 1 %), Iran (6, 3 %), the United Arab Emirates (5, 3 %), Nigeria (5, 1 %), the Great Britain (5, 1 %).

USA (22,5 %), Japan (9,35 %), China (5,65 %), South Korea (4,8 %), India (4,4 %), France (4,2 %) are leaders in the oil import.

Dependence of the developed countries on oil import currently makes about 55 % and has a growing trend. According to the estimations of experts, it can increase up to 85 % by 2030.

Alongside with the capacity of the oil market the level of the world prices for oil is also a key factor. Any long-term forecast of the world prices for oil has always been characterized by a high degree of uncertainty and all of them have failed to be true.

Table 5. Dynamics of the mid-annual world prices for oil (dollars for barrel) [2, 6]

Year	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Price	16,8	19,82	18,4	15,4	17,34	27,67	23,1	24,06	27,68	36,02	50,48

For the nearest decades it is predicted that oil will preserve its leading role in the world fuel and energy balance. Consumption of oil will increase but the rates of growth in different groups of countries will differ. On the whole the current forecasts predict average year rates of the consumption growth for the period up to 2020 at the level of 1,6 % - 2,2 %. Thus, the highest rates of the growth will be observed in developing countries and in the countries with transitional economy (2, 6 % a year). In the countries OECD (Organization for Economic Co-operation and Development) growth rates of oil consumption will be much lower (about 0, 8 %), including in the USA and Canada - 0, 1 %, in Japan - 0, 3 %. In the period up to 2020 consumption of oil only in China and India will increase up to 600 mln.t. and 280 mln. t. accordingly. Though the markets of developing countries will be the most rapidly growing, such as markets of China and India, the markets of the developed countries will keep the position due to the great volume of oil consumption, accompanied by the depletion of their own resources. So in the USA and Canada the consumption of oil will make 1240 mln. t. in 2020, and in the EU - 685 mln. t. According to the forecast International Energy Agency (IEA) world consumption of oil should make

5, 2 bln. t. by 2020 and 6 bln. t. by 2030 (in 2000 - 34 bln. t.).

At the nearest three decades the demand for oil and oil products will grow. Concerning to the oil supply in the world market significant changes will take place in this sector. In spite of the fact that in the developed countries-exporters of oil the extraction and export of oil will be considerably reduced, exporters assume that the world petroleum industry can provide the necessary amount of oil to satisfy the growing demand. In conditions of the increasing of world prices the world oil recovery will be still concentrated in a small number of the countries. Along with the reduction of oil extraction in the USA and the Northern Sea the role of OPEC will increase. It is expected, that the share of this organization in the future extractions will increase from 38, 4 % in 2000 (1435 mln. t.) up to 40, 4 % in 2010 (1795 mln. t.), 48, 3 % in 2020 (2510 mln.t.) and 54, 1 % in 2030 (3245 mln.t.).

The reduction of oil recovery in the OECD countries and in developing countries such as China, India, other Asian countries, and also in the countries of Latin America, except Brazil, is predicted.

The most pronounced increase in oil recovery is predicted for the CIS countries and Russia. Here the oil recovery will increase up to 695 mln. t. in 2020.

Considering the present state of oil branch, it is necessary to pay attention to the issue of oil refining.

For the last decade capacities of world oil refineries have grown by 11 %, or by 430 mln. t. per year. The basic part of growth of capacities was in Asian-Pacific region (ATR). The number of oil refineries from 1995 to 2000 grew from 705 up to 743 basically due to the new factories in Asian-Pacific region. Since 2000 the number of oil refineries in a world petroleum-refining industry has been constantly decreasing.

Some characteristics of the world petroleum-refining industry are given in Table 6 [10].

Table 6. Petroleum-refining industry of the world

Parameters	Items	1995	2000	2001	2002	2003	2004	2005
Capacity	mln. t. per year	3826	4098	4142	4178	4196	4230	4256
Volume of processing	mln. t.	3151	3446	3489	3475	3564	3686	3830
Degree of capacity usage	%	82	84	84	83	85	87	90
Number of oil refineries		705	743	732	722	717	675	661
Average capacity of oil refineries	mln. t. per year	5,4	5,5	5,7	5,8	5,8	6,3	6,4

Current capacities on oil refining are distributed among the regions of the world as follows (%): Northern America - 24, 5; ATP - 26,1; the Western Europe - 17, 6; the East Europe and the former USSR - 12, 0; South America - 7, 8; the Near East - 8, 2; Africa - 3, 8. For the last decade the share of Northern America, the Western Europe, the East Europe and the former USSR has decreased, but the share of regions ATR and the Near East has increased from 19, 4 up to 26, 1 %.

High technical level of equipment and sophisticated technology have allowed the USA increase the intensity of oil refining to 96 % - only 4 % constitute the output of boiler fuel and losses. This parameter is rather high in Canada – 96 %, Germany –

87 %, France – 86 %, the Great Britain – 85 %, Italy - 82, 5 %, Japan - about 82 % [11].

The different structure of technological processes in the world explains absolutely different output of target products of oil refining (Table 7) [10].

Table 7. Output of the basic oil products in 2005, %

Mineral oil							
	Patrol	Diesel fuel	Kerosene	Jet fuel	Boiler fuel	Liquefied oil gas	Other products
World as a whole	25,7	27,3	2,4	5,8	13,3	9,4	16,1

The rates of growth of the petrochemical industry are higher than the rates of the growth of gross domestic product (GDP). This feature is observed over almost 50-years. The data on the rates of growth of world petrochemistry are given in Table 8 [10].

Table 8. Rates of growth of world petrochemistry, %

Parameters	1990-1996 гг.	1997-2004 гг.	2005-2007 гг.
World GDP	2,9	3,1	3,1
Petrochemistry	3,8	4,6	4,7

The world petrochemistry is a major consumer of raw materials. In 2004 it required for its needs 6, 5 % of oil, including industrially developed countries 8-10 %, developing countries - 2, 5 - 5, 0 %. The total profit of petrochemical production reached about 1, 7 bln. dollars in 2004. In the USA it makes 1300 dollars per capita, in the EU countries approximately 1000 dollars, in the countries of the East Europe and the former USSR - 160 dollars.

The share of the oil-and-gas companies in the production of basic petrochemical half products makes 60-90 %, intermediate products - 40-60 %, end products - 30-40 % in total production of petrochemicals.

In the structure of the leading oil-and-gas companies of the world the share of petrochemical sectors makes: in total profit - 6-12 %, in the net profit - 6-17 %.

Today the USA has reached 26 % in the volume of global petrochemical production, the West-European countries – 30 %, Japan – 10 %, developing countries ATR – 17 %, Near-East countries – 4 %, other countries - 13 %. Now, when the analysis of the current state of oil refining has been made, we shall consider the forecast of consumption of oil products.

It is expected, that in the foreseeable future the demand for oil products will increase also by 1, 5 % a year and will reach 5, 7 bln. t. in 2030 against 3,5 bln.t. in 2000. Thus, the share of light and average distillates will grow in demand for oil products (gasoline, diesel fuel, aviakerosene). As a result by 2030 the consumption of motor kinds of oil products will make 82 % of the whole volume of consumed oil products against 78 % in 2000. The greatest growth of consumption of oil products, as well as oil, is expected in developing countries, first of all in China, India and the countries of Africa. More than 85 % of new capacities of oil refineries will be constructed in these countries and others, which are not members of OECD.

In the group of states with transitional economy, according to the forecasts of the IEA, the demand for oil products will increase by 2 - 2, 2 % a year on average.

The rates of expansion of capacities on primary oil refining, according to available forecasts, will be a little lower in comparison with the rates of growth of demand for oil products. So, according to IEA forecast, the growth of world capacities on primary oil refining in 2001-2020 will make only 1, 3 % per year on average in comparison with 3 % during 1991-2000. The decrease in the rates of growth of world capacities on processing is explained, first of all, by the development of modernization process of already available equipment. The construction of new capacities is expected mainly in economically developed states.

The growth of the share of import in covering the whole global demand for oil products can also be expected. Hence, the advancing growth of total world import demand will be kept approximately by 1, 8 - 2, 0 % a year on the average, or by 265-300 mln.t. up to 1015-1050 mln.t. in 2020.

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BIOACCUMULATION OF CANCENOGENES IN FABRICS OF THE EXHIBITED POPULATION OF THE CENTER OF FERROUS METALLURGY

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According to numerous sources of the literature as the major addition to an estimation of an exposition on the basis of monitoring pollution of an inhabitancy comparative results of an estimation of accumulation, including metals can serve, in the internal environment of an organism at inhabitants of compared territories or separate groups of the population as microelement structure of bioenvironments (blood, urine, hair, nails, a teeth, etc.) reflects total receipt of polluting substances from objects of an environment and is an objective parameter of ecological trouble (B.A.Revich, 1997, 2001; L.I.Privalova, B.A.Katsnelson, S.V.Kuzmin, etc., 2003; V.M.Boev., 2005; B. Seifert, K. Becke., K. Hoffmann et.al., 2000).

Research wet inhabitants of Magnitogorsk of different age groups has shown, that high concentration of cadmium and nickel are characteristic for all age groups with the maximal parameters exceeding an allowable level in 6,0 times (p <0,02) and 3,9 times (p <0,02) at persons of 20-25 years and 5-years age, accordingly. Guard high concentration beryllium in urine, 20-25 years exceeding an allowable level in 2,4 times, (p <0,05), that less than his minimum level of 4-years age in 8,7 times (p <0,02).

The maintenance of lead in age group of 20-25 years exceeds in 2,4 times (p <0,05) an allowable level; the minimal concentration - in group of children of 9 years. Excess of allowable age levels of the maintenance in urine chromium, arsenic, cadmium and cobalt is not revealed.

For an estimation of exposition features of a metabolism identified in urine cancerogenic substances we lead the analysis of their maintenance in different age groups.

The estimation of age features of the share contribution identified cancerogenic substances in the general cancerogenic structure urine city dwellers in view of the period biological accumulation (which maximum was compared to peak of their concentration in urine), has defined a priority cancerogenic substances in ascending order the period of their accumulation in an organism: lead, which period of accumulation in an organism has on the average made 4,2 years with the first peak of the maximal deducing from an organism in the age of 2th years at a level of concentration in urine 0,5 from allowable; strontium, average which period of accumulation 4,3 years with the maximal primary deducing with urine at 7-years age; nickel, which period of accumulation has on the average made 5,0 years with the first peak of the maximal deducing in the age of 5 years at a level of concentration in the urine, exceeding allowable in 3,9 times (p <0,02); Cobalt and beryllium, accumulations having the average period in an organism 6,0 and 6,3 years, accordingly, at the first pique of the maximal concentration in urine for cobalt in 5 years and beryllium in 2 years; cadmium, with the average period of accumulation in an organism of 12,5 years and a primary maximum level of deducing with urine in 12 years.

Taking into account the tendency of growth / decrease in levels of concentration of deducing revealed cancerogenic substances with urine during the different age periods of a life the greatest danger represent: strontium, cobalt, nickel - which dynamics of concentration in urine tended to decrease on a level of primary peak of deducing, probably, as a result of insufficient activity of enzymes protective a metabolism and amplification of processes of bioaccumulation.

Intensification at increase in an exposition of deducing from an organism with urine such cancerogenic substances as beryllium, lead, cadmium, chromium (the increase in a level of deducing in comparison with peak of their concentration in urine has made on the average 2,4 times (p <0,02), 1,5 times (p <0,05), 3,0 times (p <0,02), 1,9 times (p <0,05), accordingly, probably, it is connected to activation of enzymes of a metabolism neutralizations.

Age tendencies of concentration identified in urine cancerogenic substances, described by the polynominal equations, have allowed to predict character of deducing cancerogenic substances, indirectly determining features of their metabolism in an organism. Thus for secretory systems and an opportunity of increase in accumulation in an organism in currents of a life define the highest cancerogenic danger: strontium, lead, бериллий at enough high reliability of the revealed age tendencies (R = 0,95).

Hence, as a result of the analysis of a level of concentration, the share contribution and the age tendency of change identified in urine cancerogenic substances the greatest danger as a result of their accumulation is represented with strontium, cobalt, cadmium, nickel.

Concerning identified in urine of lead and beryllium the authentic tendency of increase of intensity of their deducing(removing) with urine in more senior age groups is marked, that, probably, is connected to activation certain protective fermental systems of an organism.

Blood is the universal liquid fabric of an organism reflecting not only морфофункциональное a condition of other bodies, systems and realizing maintenance of a homeostasis, but also total influence on an organism of polluting substances of an environment (B.A. Revich, 1990; N.F. Farashchuk, J.A. Rahmanin, 2004). In the literature there are numerous maintenances of metals given about interrelation in the surrounding and industrial environment with their maintenance(contents) in whey of blood of the person (E.A. Mozhaev, A.N. Litvinov, 1988; I.V. Mudryj, 1997; V.M. Boev, I.L. Karpenko, L.R. Salihova, etc., 2001; B.A. Revich, 2001).

Research of blood of inhabitants of Magnitogorsk on the maintenance of chemical substances identified: arsenic, cobalt, strontium, nickel, хром, бериллий, cadmium, lead which concentration did not exceed an allowable level at the maximal parameters for lead, cadmium, chromium and minimal for arsenic, strontium and beryllium.

Research of the share contribution revealed поллютантов in structure of a cancerogenic structure of blood has defined prevailing concentration of nickel in group of persons of 40-49 years; strontium and cobalt - in groups of 20-29 years and 40-49 years; chromium - in the age of 13-29 years and 40-49 years; beryllium and cadmium - in 13-19 years and 50-59 years, lead - during 30-39 years age.

The analysis of the age tendency of concentration identified in blood cancerogenic substances has revealed disposable rise of concentration of lead in age group of 30-39 years with the tendency of decrease in more advanced ages, that, probably, is caused by the long period of his accumulation and activation specific protective systems of an organism; two-single rises of concentration through the 20-years period of strontium, chromium; cobalt and cadmium in 13 and 30 years; thrice rise of concentration beryllium through a 20-years interval (10; 30 and 50 years).

Authentic dependence of growth of concentration of nickel in blood with increase in age is received. The revealed features, probably, reflect, waviness of character of activization certain protective fermental systems in an organism of the person, one of making active which factors is the level of concentration of elements in fabrics - targets and in blood. Thus wave character of change of concentration in blood considerably differs from character of their changes in urine where the periods of increase are observed more often, defining thus the big biological sensitivity and reactance of the given fabric of the organism, carrying out adjusting function system of maintenance of a constancy of blood, as internal environment of an organism.

Hence, it is possible to assume, that the raised(increased) level of concentration cancerogenic substances in blood reflects infringements of a metabolism of adaptive reactions, their increase in urine - defines a degree of intensity of the given processes in reply to negative influence of environment. In this connection, established close to as much as possible allowable levels of concentration in blood of lead, chromium and cobalt (the maximal concentration of lead exceed allowable in 2,4 times, $p < 0,05$) at existing deficiency of their deducing with urine and the high maintenance in objects of an environment, define infringements participating in a metabolism their structures, the population causing high health hazard, growing during a life.

Close to as much as possible allowable to concentration of cadmium and nickel in blood on

a background of their intensive deducing with urine and the high maintenance in objects of OS, presumably, define their raised receipt in an organism, activate metabolic processes during all life with critically dangerous periods in 13-19 years and 50-59 years.

Significant growth of desease by malignant new growths of reproductive sphere, "early development " a cancer and increase in values of relative risk of diseases at young age of women, no less than a significant gain of desease a cancer dairy iron for the period of research (on 74 %; in the Russian Federation the gain of desease a cancer dairy iron for this period has made 46,3 %, V.V. Dvojrin with co-authors, 1994), allow the basis to assume about the importance of the cumulative remote cancerogenic effect on a background of reproductive infringements at the women living in conditions strong anthropogenesis of influence on a population.

From 36 various risk factors and the patients distributed in groups with a cancer dairy iron and healthy women, on size of factor ранговой correlations and to character of communication(connection) of each factor with disease of a cancer dairy iron us it is established the basic 9 factors: cancerogenic substances chemical substances, the temperature factor in conditions of manufacture on a background oppression immunity; age; spontaneous abortions; background diseases dairy iron, фибромиома a uterus; diseases of a thyroid gland; environmental contamination; primary bareness; birth of children dead; congenital developmental anomalies and congenital anomalies at children; alcohol; smoking. Other factors of reproductive character have direct, but weak communication with development of a cancer dairy iron.

Thus, the significant risk of development of a cancer dairy iron defines the polyfactor: a combination external (cancerogenic substances, косancerogenic substances and high temperature); internal (background diseases dairy iron; from reproductive infringements is a primary bareness, spontaneous abortions on a background of high concentration пролактина in whey of blood. The high maintenance prolactinium in blood it is possible to attribute to the conditions determining internal origin a risk of development of a cancer dairy iron and a cancer of genitals at women of reproductive age.

The role external chemical factors of an environment in development of a cancer dairy iron and a share of the contribution of industrial adverse factors in a level of desease by a cancer dairy iron in V.S. Koshkinoj's works (1989) is established and shown. On model of working women of Magnitogorsk metallurgical combine. On workplaces gradation of concentration cancerogenic and коканцерогенных substances are established; time of an exposition to separate and to a complex of chemical compounds. The correlation analysis, carried out to it in group of patients with a cancer dairy iron has revealed dependence between age, when the tumour and 16-¯ by factors of them 124 (professional and nonprofessional) factorial attributes is found out. With the help of the mathematical factorial analysis the share of the contribution to formation of desease by a cancer dairy iron by a cancer dairy iron sets of such attributes, as a multicomponent dust, benzo(a)pyrene, oxides of the nitrogen, equal 22 % is determined; chronic background diseases and influence pairs toluene, benzene - 12 %. Time of an exposition when the tumour has been found out in working women of metallurgical combine - 19,5 years.

Trades of women among which the cancer dairy iron was registered is stackers of a fire-resistant brick, formers in foundry manufacture, drivers the crane, operators in manufacture of hot hire. Persons of these trades subject to a multicomponent dust with excess of maximum concentration limit in 92 times, the basic component of an industrial dust - oxides of iron, make up to 84 % in the general structure of components; to oxides of nitrogen, which excess of maximum concentration limits on workplaces in 1,5 times; to benzo(a)pyrene in concentration 231-327 maximum concentration limits; to pairs toluene, пиридина; to high temperature (up to 50° C).

At studying trades of women among the urban population, fallen ill with a cancer dairy iron, a cancer of a body of a uterus and яичников are teachers, tutors, bookkeepers, medical workers, sellers, handymen.

In 1998 desease a cancer dairy iron (without workers of a metal works) has made women of urban population 88,01 on 100000, desease of working women of combine, accordingly 170,00, i.e. at working women of combine of the same age group (29-49 years) the parameter is higher almost in 2 times ($p < 0,01$).

The given fact is, in our opinion, conclusive argument for the benefit of a recognition the basic factors of an environment (especially industrial) on a background of chronic diseases with infringement of reproductive function, in development of malignant new growths dairy iron.

From histologic forms of a cancer dairy iron meets hypostasis (38,4 %) more often, ferruterous (21,2 %), not so are rare low differentiation with flat cells and moderately differentiated - 6,4 %.

With flat cells, a cancer is diagnosed for the persons working at metallurgical combine: drivers the crane, operators the machine tool hot hire, the working woman of tracks at a factory, the controllers who are carrying out the technical control over quality of hot hire. They are women in the age of from 35 until 47 years, worked on manufacture from 13 until 25 years.

Our data will be coordinated to results of epidemiological research of V.S. Koshkinoj (1989) which has come to a conclusion, that feature of new growths dairy iron at working women of metallurgical combine is the greater percent (7,4) with flat cells of a cancer. N.A. Kraevsky carried given form malignant new growths to meets seldom.

Let's note, that the persons who were fallen ill with a cancer dairy iron, were exposed in conditions of manufacture to influence not only chemical cancerogenic substances and кocancerogenic substances, but also such nonspecific factors, as high temperature and radiant heat.

Testing of chemical elements in healthy and tumoral fabrics dairy iron inhabitants of city has shown high concentration (mkg / kg) of 23 elements both in healthy, and in tumoral fabrics. The straight line, strong communication is received (r = 0,80) between a cancer dairy iron and influence chemical cancerogenic substances, кocancerogenic substances, high temperature, radiant heat in conditions of manufacture on a background oppression immunity.

Probably, the temperature factor and change of the immune status were the basic conditions of display of the cancerogenic mechanism at women. The straight line, strong communication is received between a cancer dairy iron and such factors, as age (r = 0,80), spontaneous abortions (r = 0,70), background diseases dairy iron, a uterus (r = 0,70). The straight line, average communication is found out between a cancer dairy iron and disease of a thyroid gland (r = 0,60), environmental contamination and a cancer dairy iron (r = 0,60), primary barreness and a cancer dairy iron a cancer dairy iron (r = 0,60).

The highest maintenance is established Ag, As, Si, Sb. Cr, Cd, Pb, Be, Fe, thus a difference of concentration Ag, Cr, Be, Cd, Pb, Fe in healthy and tumoral fabrics authentically does not differ (p > 0,05). In a tumoral fabric dairy iron are established authentically above (p <0,05), than in a ealthy fabric the maintenance of zirconium, magnesium, silicon, arsenic. In this connection, the cancer airy iron in conditions anthropogenous on a population can be considered influences as the remote bioeffect of an exposition ecological and to production factors: conventional to cancerogenic substances (Ni, Cr, Be, As, Cd, Fe, Zr) and a number of other chemical elements (Si, Pb,) which probably cause precancerogenic damage of a fabric up to malignant regeneration, cause changes immune system on type oppression at women. Results of research will form a basis of formation of groups of risk with the purpose of the prevention of development of a cancer dairy iron at women of young age.

As direct correlation communication of average force (r = 0,6) between a cancer dairy iron and environmental contaminations outside of manufacture is received, but the high maintenance of various chemical elements in fabrics dairy iron inhabitants of a city population which section material was investigated, probably, this number surveyed is not enough to attribute a cancer dairy iron a cancer dairy iron to ecologically caused diseases.

Thus, at planning and carrying out of the actions directed on preventive maintenance of malignant new growths, it is necessary to form groups of risk that demands their preventive diagnostics, diagnostics of primary infringements of a metabolism of adaptive systems and application of various improving measures on restoration of a metabolism that will promote the prevention of malignant new growths.

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ROLE OF SCIENCE IN MILITARY INDUSTRIAL COMPLEX DEVELOPMENT IN POSTWAR USSR

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Practice of branches of Defence industry of the USSR shows that its commodity production was always in the atmosphere of hard visible and invisible competition with technologies and sciences of Lead Nations of the world. The state had to cause material and technical, finance and human resources to coincide with their's.

The same situation was in the science field, the role of which in creation of Nation's MIC is great.

In the postwar scientific research were mainly conducted in the USSR in three large scale systems:

1. In Academies of Sciences (AS USSR, 8 Republican AS, Academy of Agricultural Sciences, Academy of Pedagogical Sciences).

2. In industrial institutes of people's commissariats (ministries).

3. In Higher Educational Institutions and Science-Research Institutes at Universities and other Higher Educational Institutions.

Of course, in some specific cases, as the work advanced, deep technological elaboration of this or that problem could be carried out in the Academies and, vise versa, some results of greater theoretical and practical value could be obtained and really were obtained in the industrial institutes. However, the basic character of the work was: theoretic – in the Academies, scientific and engineering – in the industrial Research and Development Establishments and construction departments.

Higher School took up an interim position depending on the orientation of the Higher Educational Institution – the research work carried out there could have either theoretical or purely technological deviation.

In the opinion of Professor Sergey Petrovich Kapitsa there are two forms of science militarization.

The first one – is evident, when scientists invent some new weapon; their initiative being leading. It happened so during the First World War with a chemical weapon, when F. Haber, well-known for elaborating tied nitrogen synthesis, suggested using toxic gases. It happened so later, when scientists of a range of countries proceeded to creating a nuclear weapon. All these are samples of active militarization, into which tens and hundreds of collectives and many prominent scientists in different stages of their professional life turn out to be involved. In our country, actually, a whole estate of scientific workers connected with military industrial complex was created.

But there is also an indirect science militarization, when with the help of MIC programs in the field of high energy physics, near space, far planets' and other worlds' research, thermonuclear synthesis, which won't give direct application to the Defence in the observable future.

In the postwar the Soviet Government strongly increased material expenses for science development. As for the budgeting of the Academy of Sciences of the USSR itself, it is the MIC of the USSR through which up to 30% of the budget (according to some data – even more) of the Academy was formed (according to some data – even more).

A considerable part of the means was destined to fundamental and basic research for the military branch, bypassing the Defence Department, i.e. for account of other items of the National budget somehow associated with the MIC.

Against the background of the reduction of war production colossal means were spent by the Government on research activities, development of advanced models of weapon (nuclear weapon, rockets, jet aviation, radar ranging).

It is this very time (the second part of the 40-s-the beginning of the 50-s of the 20th century) since when the cooperative behaviour in the context of military equipment and weapons development between the academic and industrial Research and Development Establishments, all kinds of construction departments and branches of war industry became closer and more purposeful.

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PROGRAM GOAL MANAGEMENT OF EDUCATIONAL WORK IN INSTITUTE OF HIGHER EDUCATION

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PGM becomes more popular, as one of the method of running the University. Using it, one can increase the probability of successful fulfillment of each particular direction of development organization. It is especially essential when each direction is a strategic priority of organization development.
The basic features of PGM of university educational work, methodology of its using, and the main advantages are viewed in this article.
Tomsk Polytechnic University has several program of innovation development. One of such program is improving the educational work. The practical realization of basic principles of PGM implements on accomplishment this very program.

The system approach of running the University involves different methods of management. One of such method is program goal management (PGM). Using it. one can increase the probability of successful fulfillment of each particular direction of development organization. It is especially essential when each direction is a strategic priority of organization development.

Using PG method especially effective when it is required to accelerate the solving of different problems. For examples, providing educational activity by necessary and sufficient resources and developing new managerial and educational technology [1, 2, 3].

Development of educational work according to the PGM can be characterized by different features. These features help to reveal and understand the main point of such development, filled with general ideas of top managers, and reconstruct the process of education in accordance with prospective goals and indicators of its achievement [1. 2. 3].

The examples of these features are:

1 Orientation of education to reaching the certain results.
2. Purposeful aspiration of education from existing state to wishful one It can help to change the external and internal environments of educational institution.
3. The development of University with help of PGM has its time limits. Every program has its beginning and ending. It allows accumulating the resources on each stages of certain educational project implantation.
4. Financial and material support of educational process in University is closely connected with budgeting. More over, when one plans the items of next period budget, it is necessary to consider the priority of realized in University program.
5. The development if University by PGM is always innovative.
6. Every action in Program should be providing by personnel. That's why it stimulates the qualitative personnel selection and its development.
7. The program of educational work development in University is closely connected with program of other sphere's development.

So, the program of educational work development in University consists of different interconnected action for reaching

certain strategic aims, when the time, financial, and material resources are limited.

The PGM is a method where the top managers of University try to reach the certain aims in educational work development. It can be realized using the stage - by - stage mechanism. First stage is forming the hierarchy of goals. The second one is elaboration the list of interconnected actions, which forms the program of development. The third one is creating the mechanism of program realization. The fours one is forming the system of controlling and monitoring the program

In general, the creation of development program includes forming the: stages of program, and mechanism of maintaining the reaching goals process. But, the program of education development is not just a sum of interconnected actions. It is a system of correlated measures which results in synergetic effect.

Program can be characterized by the number of features:

1. *Integrity.* One of the main feature, which stimulates for increasing of effectiveness of managerial work in University. It can be realized through the correlation between goals, objectives and actions.
2. *Actuality.* Program should solve the most important problems of educational sphere development.
3. *Predictability.* It means that goal should consider not only requirements of this day, but the prospective ones.
4. *Rationality.* It means that goal and the ways of its achievement, considering all available resources, help to get the maximum result.
5. *Correspondence with reality.* The program should provide the correspondence between wishful and possible state of educational work, considering limits of resources.
6. *Controllability.* It means existence not only final general goal, but intermediate ones to control the correspondence of every- results to final goal.
7. *Sensitivity to faultiness.* It is feature, which helps to reveal the forthcoming threats for accomplishing planned aims and definite deviation real state from panning one The more program detailed the more sensitivity to faultiness and distance between check points lower. Sensitivity allows managers of University to posses enough time for making decision in case of faultiness.

PGM can be successfully realized in every stage of management. In the stage of planning of University educational work PGM provide orientation of the plan to accomplish final results. PGM allows correlating the available resources to the interconnected actions of program. In the stage of organizing of educational process management PGM helps to achieve essential interaction and cooperation between the head of department, head of institution and other supervisors and executor of every planning actions In the motivation stage PGM supposes leading in University the remuneration system depending on reached results More over**,** PGM increase the effectiveness of controlling, because all necessary resources and time for execution of every action are definite.

The realization of PGM in University is actual in following cases: - Realization of certain development program, which is connected with purposeful distribution of resources;

-Forming a new terms of functioning of research and development system elements;

-When it is necessary to concentrate forces for quick recovery of organization and developing educational process;

-Orientation to final results, which leads to quickly solving the problems and mobilize available reserves of University

-Necessary coordination of subsystem goals to main goal of organization (for example, education work development

program and complex university development program)

-Improvement of management system of University

-Changing the strategic plan of University development

-Realization of educational system reform

Practical value of PGM in University is obvious, because it helps to reveal the key problems of development. Also PGM provides process of forming strategic goals and objectives and its effective reaching. The great effect is accomplished by decreasing some functions of top management in favor of realization of strategic goals.

The complex program, which is called "Improvement of educational work in Tomsk Polytechnic University", is a part of complex development program of University Goal of this programis creating and realization educational program of high quality. Other goal is studying and retraining specialists of world level, who oriented on creating competitive products and making positive changes in economy of the Country.

The program of educational work improvement in University has a number of priority goals. Realization of these goals can be controlled by the special indicators (see Figure 1).Management system of educational work, corresponding to Innovative University has a number of following requirements:

1. Reforming the management hierarchy of educational work;
2. Working out the legal norm of reforming;
3. Changing the structure of studying system;
4. Opening new educational program, which meets the demand of labor market;
5. Perfection the contents of educational program.

Al these requirements can be fulfilled by the realization of the next directions of development.

Perfection the technology of educational work, considering the world experience might be accomplished by different measures:

-Realization the University educational process based on credit system. It corresponds with main principles of Bologna declaration

-Increasing a number of Master's Degree programs in University; -Application the innovative technology in educational process, which can help forming the special knowledge about the professional competence area.

Forming the system of practical studying of specialists, which is correspond with requirements of labor market includes:

1. Developing the project-oriented education;
2. Increasing the role of laboratory training for developing the creativity of students;
3. Elaborating the system of probation work for students:

Opening the branch of the University in the enterprises and R&D organizations. Creating the modern monitoring system of education quality and studying specialists allows maintaining the process of rectifying errors. These errors might appear during the realization of development program. Also such system helps to efficiently react to different changes in external and internal environments. Quality management system ISO 9001-2000, which were applied in TPU, designing and modeling the block-schemes of education process help to realize the independent estimation of education quality in TPU.

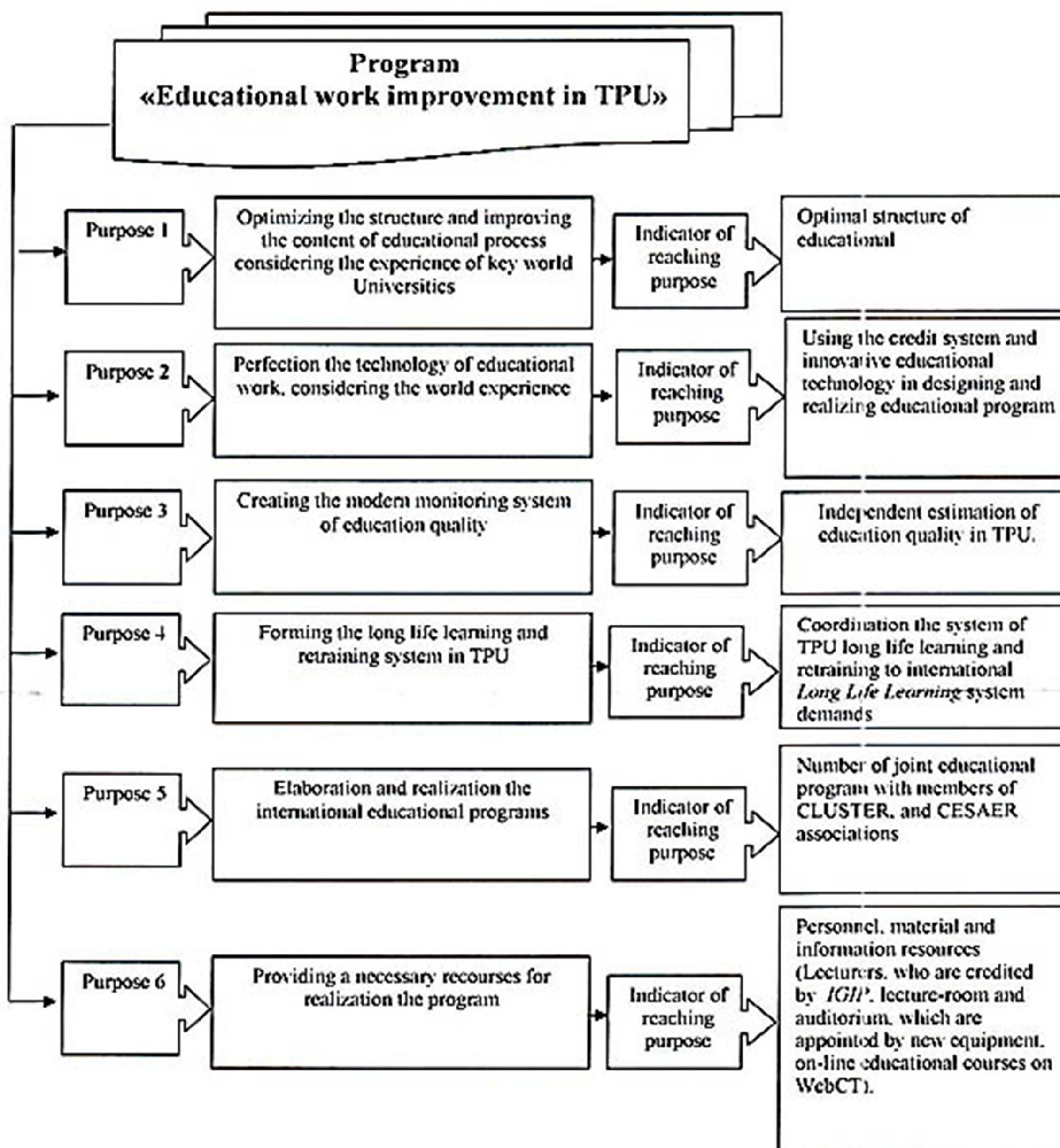

Figure 1. Realization of these goals can be controlled by the special indicators

Forming the long life learning and retraining system, includes:

■ Marketing research of regional, Russian and foreign labor markets;

■ Analyzing the demand of enterprises and its requirements to specialists;

■ Growth a number of contracts with key enterprises in sphere of cooperation in studying and retraining personnel;

■ Organizing the annual advertisement actions, Olympiads and competitions for attraction a new talented youths in University

The main tasks here are renewal the contents of distance education programs, development the system of long life learning and creating the graduators job placement system.

Elaboration and realization the international educational programs, as element of the University development program. It means the creation the educational programs which are based on credit system and experience of University - partners. The partners of TPU are Universities, which are members of CLUSTER and CESAER associations. Organizing the academic exchange of students and lecturers between TPU and other world famous Universuties.

All elements of program, which were mentioned above, need in different resources. The main resource of University is personnel. It is absolutely impossible to realize this program without continuously mastering of University personnel. That's why it is necessary to create a system of raising the levels of professional skills, improving the foreign languages skills, getting by the lectures of TPU the Cambridge certificates. Also applying new technology of educations, creating interuniversity R&D centers, and forming remuneration system for personnel are actual for realization of this very program.

Consequently, considering today's situation and future opportunities and risks, realization of educational work development program in University helps to form the recommendations about educational process changes. Also it can change the educational process, and make managers refuse from functioning project in favor of new managerial decisions. All it helps to modify the educational system in a better way.

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CLUSTER APPROACH IN MODELLING PROFESSIONALLY SUCCESFUL CREATIVE GROUP

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Nowadays we are intensively looking for both rational ways of using innovation impulses in the existing educational reality and attempts to make new approaches to realize strategies of innovation education based on the idea of development new vision of students in practical application of technologies, methods, knowledge and encouragement of their innovation activity. The main distinctive feature of modern interpretation of innovative education is that it is described as one of the factors of innovation but not as an innovation itself which should be practically applied. The value of any innovation is defined by its demand in having competitive advantage which is one of the key points in the globalization perspectives of modern economy. So all these things require quite different organization of educational process in technical higher educational establishment which should make an impulse for stimulation of innovative activities among students in terms of getting real order from industry and business on new innovation product development, technical solution, etc.

Problems associated with active search of new approaches allowing to re-think dynamically changing educational practice, should be analyzed at theoretical and methodological level. Recombination of the already known approaches to the organization of studying process has exhausted its innovative potential. Essentially new tasks aimed at forming key professional competencies, allowing to solve unusual and complicated problem in terms of uncertainty but not simple verbal interpretation of potentially significant knowledge, require new forms of organization of research practices. So, a problem of forming small creative groups arises where the members would be able to interact, feel the team spirit and effectively communicate to achieve certain goal. That is why cluster approach seems rather interesting because it allows to make typical analyses based on sociological, psychological and pedagogical data.

The idea of practical application of cluster approach to solve the problems of educational practices has its history in modern science. Though, the frequency of using this term does not always follow its meaning and theoretical character fixed by the term «cluster». There is a great variety of approaches to interpret the meaning of the term. According to modern scientific sources referring to the problems of education we can find the following approaches to cluster interpretation.

1. Cluster is interpreted as *an instrument for increasing competitiveness* of educational system. This position is presented in detail by Mr. Zakherevitch V. (1), the Head of South Federal University, supposing that forming of interacting groups, teams, organizations including universities, branches and institutions would be able to increase national and regional competitiveness on the global market. Cluster can be on regional, city and district scale. The role of university, which is meant as a higher educational establishment of innovative and entrepreneurial type, means to provide cluster participants with innovations and highly qualified specialists. According to Mr. Zakharevitch, active participation of business will stimulate cluster development and encourage forming of innovative zone development around universities as it takes place in many foreign countries.

2. Cluster is interpreted as a group formed as a result of application of technical procedures used to combine objects and people similar on two or more professional characteristics. A cluster analysis is *an instrument for typology* resulted in finding a certain number of clusters (2). There are several algorithms for cluster analysis, presented in computer statistical programs. The most popular one is SPSS 8.0.(3). This point of view is described in the research works on pedagogy and psychology. So, Fedotova O. (4) described clusters of university and school teachers combined to investigate

multilevel problems for reforming our education system, presented her ideas in tree diagram (dendrogram) and designed the mechanism of their interaction. Mikhailova O. (5) exposed groups of people according to their values and standards, which helped to identify some clusters combining people with certain defects of their evaluation of other people in general or towards women.

3. Cluster is also interpreted as analysis of electronic structure of different crystal substances. «Cluster is a group of atoms of a crystal, located on the circles of different radius with the same centre and tied up by some kind of reaction» (6). Cluster approach is interpreted as a *selective method* of modern research science which allows to simulate the object reflecting its features with the help of its small copy. Cluster taken as its physical projection becomes its prototype to create the working program for high school.

So, today there is no unified interpretation of what a cluster is, its meaning and standards of practical application in theory and practice of education. Though, these positions can be combined by referring to the same term which is actively used in professional and pedagogical sphere.

The first two positions described above are based on instrumental interpretation of cluster approach to solve problems in sphere of education. They are combined on the idea of grouping certain objects on the level of their social type non-hierarchy character. The differences are in the scale and similarity of objects, covered by cluster and a target for further classification procedures. The second theoretical approach is an attempt of studying process optimization based on analog method. Designing of program cluster on the approach in physics is in the beginning of its theoretical development.

The scientific and research project «Cluster application as the methodological principle of stimulating innovative activity of students», which is being realized within targeted analytical program «Development of scientific potential of High School (2006-2008)» aimed at finding the optimal mix of creative groups of students, makes the problems of interpretation of theoretical and methodological foundations relevant to further scientific research.

We suppose that Mr. Zakharevitch views logically give format for the requirements of business, acting as a potential employer. The concept of distribution the data (interviewees, subjects, content and topical cases) into the homogeneous groups according to their similarity, which makes the theoretical foundation of the second position, seems rather interesting. According to the views described above we can formulate the general definition of cluster which is groups (of people, specialists, students) homogeneous on their professional skills and similar on general and special abilities. We interpret cauterization as a process of combining people (participants of studying process, technical specialists, students, etc.) into homogeneous groups according to their professional trends, targets, general and special abilities ready to solve innovative tasks on the base of mutual interests of designers and consumers.

Another important thing for our research is the definition of cluster parameters, which are dispersion, density, sizes, shapes, detachability, and the problem of integral parameters and indicators that allow to make cluster analysis.

According to the tasks of our research the structural cluster elements are professional and personal characteristics of a person.

Initially we have formulated the basic principles for choosing characteristics which will become the structural cluster elements:

1. The described parameters should reveal such characteristics of a person that would allow working in a group effectively. Under effective work we understand such a situation in which cooperative work of people is more effective than the sum of their individual activities. It is necessary to follow this principle to achieve the main goal that is to form creative groups for effective innovation activity on the base of clusters that requires not individual but group approach in problem solving.
2. The described parameters should reveal the person's creative potential and those aspects of knowledge where this potential could be realized to the full. Under creative potential we mean the hidden ability of a person to create something new. It is necessary to follow the second principle to create various groups according to their creative and

professional abilities, which would give them the opportunity to solve different problems on the base of synergy effect.

Following the principles mentioned above let us hypothetically define four groups of characteristics for forming professional and personal clusters.

The first group of characteristics means professional growth of a person. Here we take into account such personal aspects which describe the main types of specialisms, according to which the students are trained in the higher educational establishment.

The second group of characteristics means creative abilities. The base for outlining this group of characteristics is the combination of verbal and non-verbal indicators of personal creativity level.

The third group of characteristics is the peculiarities of exchanging information between a person and environment. Logically we defined this group of characteristics on the results of research of students with the help of social and typical methods.

The fourth group of characteristics means the way of personal perception of a group.

The method of description for such characteristics includes the following stages:

1. We suppose that it is possible to use a certain personal characteristic as a structural element of designing clusters.
2. The analysis is made to evaluate theoretically the peculiarities of a certain characteristic.
3. We formulate the reasons and factors which served as a base to define these very characteristics among others.
4. We formulate clear definition of a certain characteristic.
5. We describe some alternative forms for a certain characteristic if any.
6. We define criteria that allow choosing theoretically that alternative form of a person characteristic that suits the best our aims and tasks of the project.
7. According to the given criteria we select one of the forms of a person characteristic.
8. Then we choose methods which could give quantitative assessment of a chosen characteristic.
9. We experimentally research the parameters of a characteristic on a certain group of people.
10. We make conclusion on the relevance of this characteristic for forming clusters and make recommendations based on quality and quantity analysis.

All the participants of the creative groups have lots of benefits from new type of links: there is free mutually interesting exchange of information and quick dissemination of innovations on all possible contacts. The participants of a team from different clusters speed up its development, stimulate innovative work of the whole team, provide with opportunities for implementing new ideas and strategies. Links inside cluster sometimes very unpredictable lead to the new ways in improvement not only innovative but educational activity and give new opportunities because of new combinations of people resources and ideas.

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SPECIFITY OF INTEGRATION OF EDUCATIONAL PROGRAMS IN CROSS-BORDERLAND REGION

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The article analyses possibilities to integrate educational programs of universities situated in different countries. The authors reveal problems that managers could face in realization of the integration.

Among modern tendencies of the world's development there is one that excels among the others. It is the dynamically growing in strength tendency of education internationalization that is manifested in: in the role of international collaboration in the sphere of delivering and exporting educational services, and also in creation of inter- and transnational institutions, organizations, centers, investment programs and funds to optimize this activities.

The Higher Education Internationalization represents an objective and dynamically developing process which steps into a new quality integration stage and is characterized by a global integration of national educational systems on the basis of maintaining original traditions.

Education Internationalization is exhorted to build a model of educational network interconnections in correspondence with the demands of socio-cultural environment. The effective projecting of educational space considering social particularity of a cross-borderland region is the most important way of optimization and development of economics and national-cultural and historical traditions of the region; value system formation that provides social and political stability of the cross-borderland region. The education, international social educational establishments and institutions oriented on the countries of our cross-borderland region is the basis of formation and strengthening the systems being formed under the influence of cross-borderland relations.

All this determines the work of a cross-borderland Higher School that is to be accompanied with the:

- integration of a "productive", social and organizational infrastructures of the given space development;
- integration of educational institutions' activities;
- working out the ideology of the future region's social image;
- educational market demands' control;
- changing of scale and specialists' training in the region.

The Higher School faces a double ambition which is characterized with social and personality levels. For the society, first of all, it is in training highly qualified specialists. Relative to a person, it is the creation of possibilities for self-realization and providing a necessary social status.

This multilevel ambition determines the following functions of the Higher School: regulation of the activities associated with delivering knowledge necessary for performing highly qualified intellectual activity; providing the possibilities of definite layers' and communities' reproduction; creation of conditions for assimilation of socio-cultural norms of the society by a human-being (socialization).

All the above said determines the conception of the development of ZabSHPU during the nearest ten years in the sphere of delivering educational services of the new type. The opening of a Transnational University in the Eastern Transbaikalian cross-borderland region can become such a social educational institution that will be able to promote deepening the processes of international integration.

The concept of the new educational institution supposes the creation of maximally favorable conditions for the educational services' export expansion and the academic mobility of the students and teachers.

Zabaikalsky State Humanitarian-Pedagogical University named after Chernyshevsky N.G. has got steady suppositions and a special experience in teaching foreign students (from China, Mongolia, Turkey etc.). During the last ten years more than a hundred of students from China and Mongolia had studied at different faculties of the University on the basis of corrected curricula and got double diplomas. Under modern circumstances the realization of educational process on the conditions of creating a cross-borderland educational institution is becoming more urgent.

The main purpose of creating a new educational institution is satisfaction of the cross-borderland region's increasing demands for highly qualified specialists; providing qualified teaching students who are getting professional training with maximal retaining of national educational systems' peculiarities in correspondence with the demands of the world's standards which are competitive in the labour market.

The realization of this purpose is possible with solving the following problems:

- the formation of adequate to modern level of the civilization development knowledge about the nature, human being, problems of the environment and the society of the cross-borderland region;
- the achievement of the correspondence of the students' knowledge to the world's level of general and professional training and culture;
- the integration of a person into the world's and nation's system of culture under the new conditions of existence in the conditions of a cross-borderland region, involvement into a unified historic, social and economic and cultural context;
- the development of ability of the students to a "horizontal" dialog (intercultural, interlingua, social one and etc.) in the interests of strengthening civil peace, of collaboration and development in the region.

The main activities of the University projected are:

- the organization and carrying out the educational process in the sphere of Higher Professional Education within the frame of license to have the right to perform educational activities;
- the creation of a unified evaluation system of students' knowledge and nettings of academic disciplines;
- the elaboration of linked curricula which provide fulfilling of educational standards of both countries;
- providing getting two/double diplomas;
- the elaboration and introduction of active and intensive training methods and knowledge quality monitoring into the academic process;
- carrying out the procedure of recognition and establishment of educational documents' (ED) equivalence for the citizens of foreign countries and also of the University ED legalization;
- the research activities on mutual agreed programs with academic and educational institutions of the countries, Academies of Sciences and Academic Communities on theoretical and applied problems;
- the creation and exploitation of informative-intellectual resource bank of scientific ideas, software support and information systems of neighboring states;
- financial and economical activities;
- the organization and performing regional and international exhibitions, seminars and conferences.

The creation of the University will need to solve the following problems:

- the accumulation of organizational, managerial, scientific, financial, material-technical and personnel resources;
- the creation of ideology, language politics and concept of the University by means of international like-minded people collective formation;
- the elaboration of a unified educational system (determination of structure of standard contents, curricula, programs, forms and technologies of teaching), evaluation of teaching quality and appraisal forms of graduates (credit system);
- the determination of the diploma and its supplement status, its nostrification and convertibility;
- achieving competency of the graduates on the labour market and their possibility of further job placement not only in a cross-borderland region but all over the world.

Let us consider aspects of the given problems – the structure and content of the educational standards, the evaluation of education quality and appraisal forms of graduates (credit system).

The existing State educational standards in Russia include both federal and regional components. If the federal component of the State standards provides the unity of the educational space of the country, then the regional one considers the specifity of the region. The educational standard of a cross-borderland University probably should involve the following components:

- international;
- national;
- sub-regional (cross-borderland) which in this case will be more global than national.

If the first component of the standard provides the correspondence of the educational content to the international standards, the second one does the correspondence to the interests of the member-countries.

The sub-regional component is considered to be a complex of disciplines of the academic curriculum within the frame of the formally established agreement between some Universities with the purpose of coordination and stimulation of qualified collaboration in the contracted fields (education, management, ecology, tourism and others). The sub-regional component should consider natural, socio-cultural and economical specifity of a cross-borderland region; provide the educational system's orientation on cross-border territorial interests and market demands.

When projecting the component of the educational standard of a Transnational University, it is necessary to find answers to the following questions: how to refer the educational standard components of a Transnational University to the components of educational standards of the member-countries; what should be the content filling of the above numerated components; what is the time correlation allowed for their consideration; what are the sources of scientific, methodic and resource provision of the educational process?

Providing educational standards is realized in the quality evaluation of the education got. The results of education quality control are expressed in its evaluation. Being founded on the control data, the evaluation should consider the efficiency of all kinds of learning-cognitive activity; characterize fullness and quality of knowledge digestion, consciousness of their digestion, presence of general and specific knowledge and skills for a given subject.

The Higher School integration in Russia, China, Mongolia into pan-European educational system, the development of a multilevel system of professional education make us revise the existing evaluation system in Russian Higher School. As an alternative to the existing five-grade evaluation system it is offered to consider a credit (or unit) evaluation system which has been used in Higher Schools of China and Mongolia.

The existing models of credit systems can be referred to the two main types:

- credit systems oriented generally on credit accumulation;
- credit systems oriented generally on credit examination with the purpose of providing academic mobility.

In China credit-examination systems are used. They, as a rule, are based on the notion and definition of credit as an evaluation unit of labour contributions on the development of the educational program as a whole or a part of it. Credit-accumulation systems mainly define credit as an evaluation unit of the development results of the educational programs – the acquired knowledge and skills.

The systems oriented on the evaluation of the planned results of the educational programs development, and not labour contributions, seem to us to be more attractive. The accumulation evaluation system involves the variability of the results of education, promotes the manifestation of individual-personal features of students. It stimulates the methodical work of the student, excludes the subjectivism of the teacher. If we think that a credit is a unit of a quantitative volume measurement of the education got (credit units), then, basing on the average labour contribution, using credits will only come to a conversion of labour contribution of hours allowed to study a discipline into credits or credit units. In such a presentation, as some research workers note, the credit system gives absolutely nothing for the educational system. That is why, when evaluating the education quality in the planned Transnational University, it is necessary to come out from the fact that a credit is not only labour contributions of a student, but also the evaluation of the results of the educational program, i.e. one should use credit-accumulation credits.

What difficulties will one have to overcome when introducing the given credit system? The analysis of literature and the experience on linking curricula on the given problem allows formulating some important statements which, in our point of view, will result in revising general approaches to the academic work organization in the projected University.

1. It is necessary to enlarge courses. To join together not only themes of allied subjects, but also read integrated courses.

2. It is necessary to reduce the quantity of auditorium hours making accent on solitary work. To use auditorium hours to study problem questions of the course, hold panel discussions, seminars and not to translate information.
3. It is necessary to organize the solitary work of students in a new way. The solitary work of students should have: a controlled character (according to the development of students' readiness to solitary work the original direct leadership of the teacher passes over the mediated leadership to autonomy); problem character (creation of task system teaching students to search, analyse and information interpretation); structural character (it should correspond to the structure of the academic activity and have an approximate, performing and controlling parts; a tendency to intensify the current and ease the result control being manifested); an individual character (to take into account the individualization principle).
4. It is necessary to introduce a module time-table of the educational process, having reduced the number of simultaneously studied disciplines; the dipping method on special subjects is possible.
5. It is necessary to work out and introduce integrated cross-disciplinary activity types. Cross-disciplinary term papers, business-games, group research projects, etc., which will train students to write qualitative graduate and thesis works.
6. It is necessary to use widely an independent examination on the very different grade levels in the form of public defence of term papers, student teaching reports, research projects, when the work done is evaluated and the questions are asked by students themselves or teachers who didn't the given course.

Introducing a credit system supposes not only changing the accounting unit of labour contribution of the educational programs' development, but also reorganization of the academic process.

The reorganization of the academic process is aimed to provide for a student a freedom to choose an individual educational trajectory which is defined by the individual curriculum; activation of cognitive activity of students and development of capability to self-administration of their cognitive activity.

Effective projecting of educational space considering all the specific features of a cross-borderland region is the most important way to retain and develop economics, national-cultural and historical traditions of the region; to create a basic value system providing social and political stability of the region. Now-a-days the realization of the given tendency of work is carried out. So, the Protocol of the intents to make a combined institution of a transnational type is signed between Zab SHPU and the Administration of the city of Manchzhuriya.

In general, the education internationalization, being the key direction of educational policy and the means of development of all cross-borderland region's life is exhorted to build the system of interconnections of education and socio-cultural environment.

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VIOLENCE, AGGRESSION AND EXTREMISM: IN NATURE AND SOCIETY

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People usually fear for violence and hate it, although some of them also can unaccountably admire for it. Such mixture of these feelings shows that this phenomenon originated from the bottom of human soul. We are often in such emotional state when interpret it but it's important to rationalize it.

Violence is often identified with only its rude physical, political and religious forms. However there are many other forms of behavior and consciousness that belong to violence but most can't recognize it as a rule. There are everyday occurrences such as sexism, ageism, race, moral discrimination and so on.

We may say the same about aggression and extremism. So these phenomena are understood here as every abnormal behavior and thoughts of people who find their meaning of life in negation of generally accepted values and norms. It can be said that aggression and extremism are immanent side of human beings because it can be found everywhere in human life: in the relations, that based on biological specifics, in social activity and in spirit existence of people.

The specific trait of modern condition of philosophy is an aspiration for solution to the problems that come into existence between borderlines of sciences. Philosophical synthesis discovers the similar structures in dissimilar human spheres and derives some interesting conclusions from this congruence.

At present, there is not philosophical general reasoning of violence, aggression and extremism as an immanent side of human beings and so we want to discuss the following questions: What is general meaning of aggression in being of Life? What are differences in essence between biological and human aggression? Which factors does a stability of violence in human existence provide? What is a specific of main forms of extremism? Which functions does extremism perform?

It is well known that aggression is a common phenomenon of nature. It can be said that aggression is an active side of vitality. The general significance of aggression lies in important metaphysical fact that every creature must hold its position in being and keep a check on it. It means that self-preservation includes a specific activity. There is force that pushes competitors away from feed and chucks rivals out of one's territory. This force not only protects from others but provides its renewal in future generations thanks to sexual politics. Another inactive side of vitality is conciliation and altruism. There are the two orientations in self-fulfillment of vital energy. If it says metaphorically, aggression is a strategic defense of Life. The inter-species aggression is self-fulfillment of species on opposition from the others. The inner-species aggression optimizes the allocation of resources on species territory and one of forms of sexual selection. Aggression may be defined by "do harm to a creature".

The phenomenon of human aggression can be understood as “do to harm to a creature *intentionally*”. The primary feature of human aggressiveness is an intention or expediency. The development of consciousness radically changes some characteristics of aggression. The human race keeps of course several forms of biological aggressiveness but consciousness alters them, therefore the human aggressiveness should be understood as a new condition in comparison with the biological aggressiveness. The condition started in a unique symbolic state of existing. It is engendered by such new principal qualities as human self-identity and memory. Correspondingly, aggression transformed into action's series of long duration. There are personal intentional series or lines of conduct. The main cause of human aggression is failure to understand one another because the human symbolic world is strong segmental and autonomous. Every segment is created of daily life of some stably groups who generate its specific value's and opinion's system. Incomprehension originated from many borders between these systems and it is root cause of aggression in human beings. Human aggression became a complete conscious structure that includes modeling of forthcoming actions, justification and legitimacy. Actions are very various from insinuations to a direct physical

impact and we can see the obvious predominance of indirect symbolic forms here. Moreover, human aggression is rational, preventive and equivalent. It orients to cultural rules of particular society, but old biological features of aggressiveness remain in individual conduct of people. There are situational emotional reactions in routine life and inborn pathological forms of aggressiveness. What is a meaning of aggression in the human world? There is a permanent active redistribution in a wide spectrum of social interaction. There is the redistribution of territories, resources and zones of attention (fame, honor, love) in case of its deficiency. There, of course, peace periods in processes of a social distributions but it is rather stop-gap pauses in permanent social fight. Phases of manifest social fight simply are more transient than peace stages and so they are usually interpret like something rarer.

Extremism is constituted as a characteristic of the specific group's consciousness. We think that extremism and aggression as biological phenomenon are quite different and it can not speak that extremism has its origin direct from aggression. Relationships between extremism and aggression can be interpreted similar to connections between form and content where extremism as active conscious social form gives certain characteristic shapes for primordial aggressive activity. Extremism is aggression that is conceptualized in some group-consciousnesses. There is an unconscious formed project of life, which shows good reason for ambitious pretensions of some groups who need power, goods or fame. Extremism is always a specific form of world outlook or schemes of references. Moreover, extremism expresses a specific identity of some groups who are in situations of open disagreement with norms and values of dominant culture. Such identity manifests itself in many ways. There are defiant life style, specific clothes and its cant.

What does a historical stability of extremism determine? Forms of extreme consciousness are generated by some permanent factors. The first is an anthropological factor that is based on three forms of natural distinctions. One of them is the distinctions between men and women. Both sexes have their way of behavior and style of appreciation and thinking. The truth is that both sexes are equivalent in existentional meaning but their natural specifications historically predetermined a successful functioning in defined different sectors of human existence. This anthropological situation determines an evolution of men's domination and women's protest. Thus conflict takes roots in a primordial anthropological situation of their natural differences. The conflict is represented in the male chauvinism and radical feminism. But it must be noted that ultimate aims of sexual politics or struggle for power in love and family are the whole truth of this conflict. Another form of the anthropological factor of extremism is natural ethnic distinctions. There is radical nationalism and conflicts of ethnos. Radical nationalism often is an effective form of ethnic mobilization on the way an accelerated transformation uncertain ethnic community into nation. In generally, there are two types of radical nationalism, videlicet a "nationalism of blood" and a "nationalism of idea". In essence, there are two historical forms of radical nationalism's development. The "nationalism of blood" or ancient radical nationalism based on more a dim feeling of its inborn ethnic exclusiveness then on certain conception or ideology. The "nationalism or idea" or modern radical nationalism appeared about 2-3 centuries ago when nationalistic intellectuals and middle stratum "constructed" their standard national language, literature and identity in series of nationalistic movements, revolutions and wars in West Europe. However both can give birth to genocide in some particular historical conditions. Racism's forms of nationalism are also originated from such situations.

The third form of the anthropological factor that generates extremism is distinctions of generations. Every generation has serious distinctive features of its psychological self-organization. Teenagers or young people who are in state of very serious psychophysiological transformation into adults have a consciousness that is qualitatively different from the other ages. There are an idealistic romantic impatient consciousness and fluctuating identity. It has been long recognized that a constant conflict of generations was continued for human history. This conflict was earlier regulated by traditions however the Age of Reason ruined a faith in traditions. The young can't understand previous generations and conflicts with them. Contra-

cultures of the young are originated from these processes in the second part of XX century. The very important of them are beatniks, hippies, punks, skinheads, rappers. These contra-cultures have essential general features. All they express the same existential experience of a certain anthropological category. They realize their community and continuity of their opposed lifestyles. These contra-cultures develop in a specific musical format when their musicians are simultaneously their ideologists. Their music from rock-n-roll to hip-hop is their banner, ideology and symbol of faith.

The second fundamental cause of extremism is a social factor. Every society is organized in the hierarchic order; therefore constraint, violence and exploitation of man by man are normal natural forms of social development. They are modifications of human aggressiveness. It can be said about some typical social groups who usually can have extreme consciousness. Firstly there are new influential groups who haven't a state power yet and strive to posses it. There are also oppressed classes who struggle against dominant groups in diverse ways right up to revolt. Secondly there are diverse outsiders and marginal groups who hate a dominant culture and strive to establish their antagonistic culture. There are, for example, some criminal subcultures and new religious movements. Both types of nonconformist groups demonstrate high degree of self-isolation and hostility. Thirdly there are often critical altruistic intellectuals who feel their indignation at social unfairness and create nonconformist ideas.

The third cause of extremism is a mental factor. Consciousness of some people has tendency towards self-cultivation. A spiritual development of such consciousness creates new symbolic alternative worlds. This condition is characterized by a sharpening of idealization and alienation from the real world. As a result of those processes there is appeared specific type of intellectuals who have an unusual life motivation. There is a transcending of self-given entity or a strong desire to go beyond the limits of normal reality. Such uncommon radical attitude of mind often is typical of some philosophers, artist and religious intellectuals. Contrary to popular belief radical philosophers called in question about ideas of objective reality, social conditionality of people and general meaning of the world. It results from this it appears very strange for common people conceptions such as solipsism, anarchism and a statement of absurdity of the world. Radical artists also often set a challenge to popular norms of beauty, virtue and dominant cultural aesthetic values. It is well known that avant-gardism advances art in many historical causes. Religious intellectuals examined the confines of human knowledge and feeling in order that they attempted to express an unlimited inexpressible image and notion of Good. A development of human thinking requires extreme revolutionary ideas that can overcome old forms of life. Such extreme basic ideas are an authentic soul of extremism.

Above-mentioned factors totally determine a historical constancy of extreme views. The category of “extremism” may be defined in the following way. Extremism is actions and ideas that obviously and resolutely break norms of common life or it is well-grounded line of conduct that demonstratively confronts with usual practices of people. If we consider extremism as group phenomenon, we can add that extremism is also a specific style of some groups who create their characteristic cultures and their "symbolic universes". The meanings of such symbolic “universes” are strong contrary to views of a dominant culture. Seen as whole, extremism can be understood like specific formative structures of consciousness. There are some intentional positions that are formed and reproduced in certain social development. These structures may be including four patterns at least. The first of them is the dualistic categorization of the world meanings. The world meanings are radically divided in two sides: “good – evil”, “truth – lie”, “order – chaos” "beauty - ugliness" and so forth. People, inclined to such categorization, ascribe themselves of course as an expression of positive sides. This consciousness convinces that conflict and struggle are an immanent natural condition of the world. As a result people of extreme inclinations have a disharmonious feel of the world. They also have a lot of experience of hate and fear. The second pattern is a hyperbolic self-partiality. People of these groups pride themselves on their imaginary perfect qualities. They imagine that they are the best among people. Accordingly, they have their specific morals which work only to their own; for this reason they convince that they can cheat the other people out of their goods and to use them as servants. The third pattern is an ascription of their failure to permanent animosity of social

surroundings. Extreme consciousness dehumanizes the others because only persons of their own groups are identified with "real men". The fourth pattern is a scenario of confrontation, destruction and overcoming. In other words, that is statements of main ways of the realization of their ideals.

Now we want to raise the issue of classification of extremism. We proceed from the assumption that distinctions of various types of extremism lye most of all in a sphere of their mental specifics. Primitive forms of extreme consciousness are determined some psychological characteristics and social circumstances. As for psychology, there are, for example, ethno-centrism, egoism, hard-heartedness, brutality, intolerance and, as a result, inabilities to comprehend other people. As for social circumstances, there are ethnic conflicts, sexual and age discrimination and life's injustices. People of such state of mind spontaneously associate with each other and unite in their groups where they love themselves and hate the others. In such way they find their meaning of life because they are not able independently to formulate their aim in life. The principle here is that such groups firstly spontaneously are formed and after that the corresponding irreconcilable ideology and leaders take shape. There are radical nationalistic groups, sexists, contra cultures of the youth and some criminal communities.

By contrast spiritual forms of extreme consciousness are generated by ideas. Their authors are charismatic political and religious leaders, radical artists and philosophers. Various people here are united in attempt to carry out their characteristic ideas. It can be said that the main factors of a formation of these groups are ideals. These ideals have often evidential features of the extreme patterns. For example, there are transcendent religions, utopian ideologies, some philosophical doctrines. The meanings of such radical weltanschauungs are abstract and very symbolic. They are organized with dualistic ontological opposites: “spirit and matter”, “God and devil”, “destiny and freedom” and so on. The human spirit attempts to transcend the limits of a human fate here. Surprisingly, the majority of such consciousness' forms have similar patterns of self-organization. Extremes meet and negation of the sensible world in which we live by solipsist bear a strong resemblance to total negation of teenagers. At the same time, these forms have some serious differences. There are differences in levels of mental development. The world-outlook's patterns of primitive forms have very abstract and simple character. It means that consciousness here directs its attention at easily noticed therefore its concepts originate from prejudices and common stereotypes. In contrast, "a distance of attention" of spiritual forms is great and includes examination of many causes and factors in explanation of human beings. Duality of meanings has here dialectic character whereas primitive consciousness understands duality only like confrontation. There are different ontological bases of their world-outlook's schemes of references. The primitive consciousness unaccountably concentrates on vital and material factors as underlying principles of human life whereas mentally developed forms believe that idealistic factors of spirit create and form the human world. Finally, there are different orientations of these diverse levels of extreme consciousness. It can be said that extroversion characterizes its simple forms and introversion describes its high forms. Introversion means that mentally developed individual consciousness concentrate on self-researching and gradually recognize itself, as a result, it can identify with human beings. It generates sometimes high forms of selflessness. On the contrary, activity of primitive extreme forms directs towards achievement of group's goals like emancipation or domination whereas high forms aim to change a destiny of humanity. According to the analysis given here, the extreme views have important functions in human development. Firstly, social and spirit innovations often originate from abnormal and extreme forms of human behavior. In the course of long time they slowly transform into new norms and traditions. Secondly, extremism is an inverted order of social norms and their necessary limit. Thirdly, an extraordinary activity often is necessary form of solving of very difficult problems. For example, there may be social crisis, violent pursuits or some very fixed ideas. Finally, human history can be understood as an immanent combination of traditions and a creative criticism.

It must be noted that dominant public attitude towards extremism is rather extreme. It has been frequently maintained that extremists are villains and even inhuman monsters. I'm not sure that it is completely true. We begin to think and to act according their extremist logic and it is their win because they impose on us their views

and rules. If we could exterminate all extremists, the new extremists would appear shortly after. Paradoxically, but they are a part of our world so the world is out of order. Such world engendered and will be engendering extremism. Consequently if we want to eliminate the threat of extremism we must change our world or ourselves. The main causes of transformation of natural extremities into extremism are strong unwilling to comprehend other mental conditions and cultures, a lack of self-criticism and a refusal to waive one's privileges. A new comprehension and an interdependent changing only can convert extremism into admissible forms.

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MAIN MODELS OF VIOLENCE IN NATURAL AND SOCIAL SCIENCES

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Many people in the post Cold War world thought some time that a previous violent history had finished and we should merely decide how democracy can be forested where a democratic tradition is only embryonic. The September of 2001 gave us an evidence to suggest that we had illusions about a possible finish of a violent history. It only seemed that great misfortunes of XX century like the World Wars and totalitarianism can force people to abandon the policy of violence.

Indeed, it starts a new real renaissance of political violence as norm of settlement. It is very dangerous because people anew get into the way of common violence. As it is well known the World Wars were always preceded by local conflicts and common using of violence. It makes actual to consider a problem of violence as immanent aspect of Life and human being.

This problem is a clearly multidisciplinary status. It is explained that violence is total phenomenon of Life being and all sciences which study vitality and human being consider a subject of violence in their specific way according to their objects. Not surprisingly, there are many diverse approaches that often contradict with each other. At the same time available conceptions provide a possibility of philosophical multidisciplinary agreement and a building of general system model of violence. Let's consider the main multidisciplinary positions in respect of violence.

Interesting and important ideas were suggested by biologists. Some neurophysiologists (McLean, Delgado) state that violence is bound up with peculiarities of a brain evolution. There was a unique acceleration in a development of cerebral hemispheres while there were not practically any changes in an old biological part of the brain like medulla and cerebellum. Such situation is a cause of a permanent conflict between a power of a new appeared intellect and primordial invariable instincts. This conflict is the fundamental root of violence. Neurophysiologist A. Rain from Los-Angeles established facts of relationships between a brain activity in frontal parts and an inclination to violence. His brain tomography study of 41 prisoners who were killer showed that those people have a depressed activity of frontal parts because grey matter in these parts of their brain is less 11 % than other people. It is well also known that frontal parts of the brain function as centers of sociability and abstract thinking. Such neurophysiologic information raises a query about a necessity for a medical system of diagnosis of people inclined to violence. There is important especially for politicians who can some time come into power and use political violence. I think that a main lack of neurophysiologic explanation of violence is methodological individualism and inability to consider relationships between peculiarities of the brain and a group behavior.

Psychogeneticists (Brunner H.G., Valzally L., Kulikov A.V., Osipova D.V., Popova N.K., Egorova M.S., and Shustikova M.V.) strive to define a degree of a genetic determination of aggressive behavior in human and animals. It was proved that a conception of "one gene of aggressiveness" is unreal (Brunner) because many genes and complete genetic interactions provoke aggressiveness. Psychogeneticists establish that individual differences of aggressiveness in population are caused up to 50% by genetic peculiarities and everything else

is explained by an influence of surrounding factors. While psychogenetic studies demonstrate that exclusive surrounding factors can provoke a serious transformation of inborn mechanisms.

It is known that the genetic regulation of aggressive behavior is controlled by the monoamine systems of the brain. Situation of long-term confrontations and stresses lead to transfigurations of a functional regulation of monoamine genes. Repeated experiences of aggression and wins such so constant negative experiences of defeats bring a changing of natural genetic regulation's balance. It is getting worse an inhibition of reflexes and makes more active nerve-centers of enjoyment such so long-term negative experience can form a strategy of subordination. Pathological phenomena of a regulation of aggressive behavior originate from normal primordial mechanisms by means of an accumulation of a certain neuron-chemical changing in the brain.

As appears from the above, an influence of gene polymorphism on an inclination to aggression depends on monoamine genes transcription activity from the experience of aggression. So it can be said that psychogenetic researches give a necessary empirical material for the advancement of seminal non-speculative conceptions explaining a correlation between inclined and experiential (personal or group) parts of aggressiveness. It will enable us to define ways of possible social influence over "inner" violence for purpose of its minimizing more correctly. Biologists (Valzelly L., Eibl-Eibesfeldt I., Moyer K.E.) and ethologists (Wilson E.O., Lamsden C. J., Lorenz K., Dawkins R., Ruse M., Trivers R.L.) who analyzed a biological bases of human behavior obtained very interesting results. Reflection on their works carries inference that violence is one of fundamental factors of evolution and it is not considered as only negative power. On the one hand, violence is a necessary sequence of some conservative characteristics of primates as sexual behavior, strong social instinct and territorial imperative. There are systems of aggressive domination especially over female and other weak fellow-tribesmen. There is also a strong inclination to indoctrination as a prerequisite of self-closing group mind and behavior. From this it follows tribalism, xenophobia and double moral standards. On the other hand, violence as a readiness to come up against serious problems and difficulties is such an important value of evolution as a readiness to cooperate with fellow-tribesmen. K. Lorenz, for instance, posits that violence optimizes distribution of individuals on species' territory and consumption of available resources. Violence also optimizes natural selection by means of rejection of defective individuals. Wilson claims that there are more important indirect forms of violence in human life. There are deception and hypocrisy which are specific necessary means of organizing of human complete daily routine. A level of deception and hypocrisy is a historical compromises, reflected proportions and complication of any human community. A direct aggressiveness and primordial forms of physical domination were reduced. They were substituted for social complete skills of managing of sexuality and aggressiveness.

Finally, some sociobiologists (Alexander, Keith, and Bigelow) state that such noble and generous traits like altruism, mutual assistance, patriotism and courage are a genetic sequel of frequent wars in human history. Are they right? Where is it a dividing line between genetics and ethics? Psychological approaches are quite numerous but they have two general indications. Firstly, they derive violence from inner physiologic processes that determine social behavior. Secondly, their analysis rests on an idea that violence and aggressiveness are not self-dependent phenomena but reactions to external unfavorable circumstances. Psychologists usually have a tendency to use notions "violence" and "aggression" like identical. Freud noticed that violence is a rudiment of animal past of human beings and it is an expression of any psychological structures.

Behaviorists (Dollard J. and others) consider aggression as a consequence of frustration. Social psychologists Feshbach S. also interprets aggression as a response to frustration. It is an automatic bent. There is an expressive, hostile and instrumental aggression. Another interesting variant of frustration's approach is a conception of deprivation (Gurr. T). A readiness for violence come into existence as a result of deprivation's feelings. It should be noted that deprivation is considered as not only dispossession, imprisonment and privations but there is general reaction against some gap in the

correlation between somebody's expectations, pretensions and real possibilities. There is, for example, status's stress. All the same sociologists work out the most adequate understanding of social violence. It is taken for granted because they professionally study just a level of reality where social violence appears. By my opinion, the most interesting sociological conceptions that suggest their interpretations of causes of social violence were developed by Smelser N., Parsons T., and Huntington S. Smelser demonstrated that opposed to the existing social order political movements origin from any fundamental non-coordination of macro-social structures. Such non-coordination is a result of changing of status' correlation between main social groups. As Lenin said 100 years ago, the upper strata can't rule in the old way and lower classes want not exist in the old manner.

Parsons was firmly convinced that the prime cause of social violence is a conflict between diametrical opposed values. It starts when a break between dominant social-cultural values and main social structures had been. In comparison with "pure sociologists" Huntington suggests more global multidisciplinary approach. He combines sociology, history of civilization, culturology, economics and political science. So it appears a global context of consideration where the problem of violence also becomes global. Huntington confirms that a modernization provokes a global violence as a result an appeared gap between westernization's development of particular economies and changing of their political institutions. The global violence is generated in countries where a radical change of modernization came about. It should be specially noted that not the poor but the middle classes in developing countries are often a source of instability and violence. These middle classes of transitional societies aspire to consumption and possibilities like the middle classes of rich countries. A social mobilization and an intensification of political participating of these classes which are not yet regulated by available political structures are more important factor of instability than an uneven economic development. It sounds quite paradoxically, if we remember Aristotle's classical statement about middle classes as a basis of stability in society.

Civilization's approach gives us a union of multidisciplinary mosaic and a universal system of theoretical coordinates. It allows us to see a united world picture and general factors of development but while it is possibility a menace of new mythologizing.

Some historians (Tilly Ch., Anderson B., Giddens A.,) who study a history of wars have a tendency to consider violence and war as a necessary natural phenomenon like evolution or ecological changing. Their studies could be helpful for our research's purposes. They state that a change of historical types of wars generally corresponded to social evolution. Such co-evolution of society and its war's system was characterized by gradual democratization and technologizing. There were five qualitative stages of such development.

Firstly, there was a primitive democracy of a face to face tribal skirmish. Secondly, there were armed conflicts of skilful fighting men in ancient world. Thirdly, mercenaries of XVII-XVIII centuries joined battle against each other in European wars of "armchair strategists". Fourthly, mass armies based on compulsory military service appeared after bourgeois revolutions and war assumed a special patriotic character. Finally, an acceleration of a military-technical progress in XX century brought into existence total wars. There are wars of mutual mass extermination where distant modes of destruction prevail and emotional factors of war become atavism.

Strategic theory (Aron R., Kan G.) accounts for conflict as an object that is forced by internal and external factors determining escalation of conflict. This approach can be named "philosophy of war" because here it is considered rational modes of war's management and ways of achieving of win. They suggest that a theory of games can rationally explain a mechanism of conflict development. Actually, such approach is quite innovative sound because it attempts to expose general logical structures of conflicts irrespective of its differences. For example, some scientists (Сингер Дж., Смол М., Ричардсон Л.) derived a model of arms race from the date of trade circulation between countries and allocations for Europe countries defenses in 1815 – 1899 years. This model corroborated inevitability of the First World War but such approach was used to an analysis of the data of 1900-1945 years did not corroborate inevitability of the Two World War. Thus,

situations of conflict interactions are often difficult to understand because it is not clear which initial variable quantities are adequate for building of such models. An aspect of relationships between violence and history received specific attention in the Marxist tradition. Marx claimed that every social formation is a system of relationships of strengths and ideas between groups or classes. Phenomena of violence and domination are determined by relationships of economic exploitation. Violence plays a great role in history as its "midwife" and social revolutions are locomotives of historical development. As it is well known, Kaytsky K. explained an origin of state and classes through the instrumentally of violence and conquest.

Post-Marxist schools tend to interpret violence soon as ideological or sociological phenomena. Ideological confrontations are chiefly responsible for violence, said Mannheim. Ideologies are collective practices of thinking that have their specific mental and ontological bases. Firstly, there is a peculiar way of thinking. Secondly, there is any hierarchical system of values where some of them are considered as basic values and stand out against a background of others. Thirdly, ideologies are distinguished by obsession of such "basic values" but loyal supporters of ideologies are not conscious of it. "Sociology of domination" by P. Bourdie argues that high strata and a state don't impose their ideologies on people. Domination of ruling classes is supplemented by common consent of lower classes. There is "a symbolic domination" or an accepted social violence. Violence becomes natural and common or legitimate. Society is filled with symbolic violence and it is an immanent part of a social habitué. There is often no necessity to impose on people. They have been indoctrinated from childhood to believe only what the government tells them.

So, there are two extreme approaches to understanding of violence. Each of them has its advantages and failures. In the first broad approach violence is interpreted as suppression in its various forms. It may be both a direct physical suppression and an indirect economical, political, psychological suppression. Suppression is any limiting of conditions of personal development when causes of suppression depend on people or social institutions. So violence here is synonymous with moral evil that consist in any breach of some standards of communal life. Such approach is worth of attention because it accentuates an immanent moral aspect of violence. But on the other hand, such identification of violence with moral evil may lead to loss of a specific conceptual content of violence. Such broad approach proclaims impossibility of being of any moral justifying violence.

In the other narrow sense of the word, violence is physical or economical damage when people do harm each other. There are physical damages, murders, robberies, etc. The specific of the term of violence here is kept but it leaves out account its moral motivation. There is an unpremeditated damage, for example, in sport or, on the contrary, in the situations when people intentionally cause harm each other.

We suggest that violence could consider in respect of concepts "freedom" and "power". Power as inter-individual relations may be defined as taking a decision from someone without having consent to do so, when one will becomes stronger at the expense of another. Accordingly, violence is one of the methods providing domination of man by man. Domination may have, of course, various reasons. Firstly, there is a real superiority of will condition. For instant, it is all forms of paternalistic power. Secondly, there is a preliminary mutual agreement like authority of the state on legal grounds. Thirdly, there is violence or a power of conqueror, occupier and tyrant.

So violence is not general compulsion and damage but it is a usurpation of smb's free will an encroachment on smb's liberty. There is important that one will suppress another will by means of physical compulsion or treat of its using.

Now let us consider a genesis of violence in life of animals and a primordial condition of humans. It is worth of note that nature likes to follow the path of least resistance and don't like aimless hostility. There is beyond good and evil and violence has mainly a functional meaning here. Nature has seemingly found a balance between violence and tolerance.

It may state that it was some chief periods of violence's limiting in human history. It can be said that there was such two periods. The first

epoch of violence's limiting was a restriction of enmity between human hordes. Unbounded animosity was limited by establishing of a principle of equivalence: "an eye for an eye and a tooth for a tooth". An idea of equal retribution was the first form of a realization of justice. Justice understanding as equal punishment in blood feud is general rule in a life of ancient people. Such principle was a reasonable limit of violence and the first form of moral relationship because it led to a mutual recognition and respect between enemies. People hated their enemies but they simultaneously respected them as individuals who have equal power and can stand up for themselves. Hence it appeared such a notable phenomenon like a war according rules, when all military actions were strictly regulated. Such ancient regulated violence looks more justified than following using of moral argued violence when enemy is considered as bearer of evil and inferior creature. Moral argumentation in conflicts often leads to intensification of violence. The second qualitative leap in limiting of violence was a genesis of state. A state monopolized violence and established the specific institutions of violence. State also strived to use indirect forms of violence instead of direct. State is the different phase of social evolution when safeguarding of social security becomes a special function within general division of labor. Answer the purpose only special groups; state has the right to use violence within limits of laws. There are army and police. Using of violence becomes more reasonable and equal in rights. State also introduced another important novelty. It can forestall forthcoming violence by acting on social conditions engendering violence. In this way state substitutes direct using of violence for threat of violence. People have to behavior themselves according social rules apprehending punishment. Most of scientists who are engaged in studying of violence consider threat of violence like type of violence.

We think that state should be reckoned as only one of possible stages of human development. State's violence objectively may lead to serious moral deformations and, what is more, above mentioned features of state organization of social life can be interpreted as a factor that really strengthens common violence. Monopoly of violence leads to its surplus. A state violence is anonymous that is a consequence of establishing of the proper institution of violence. As a result, it deadens people's feeling of violence. Indirect character of the state violence that is manifested itself in manipulating public opinion and in secret exploitation leads to broadening of a sphere of real using of violence.

However, the state violence is a form of limiting of violence that may constitute prerequisites for possible overcoming of its odious displays. In connection with problem of overcoming we intend to discuss a theme of non-violence.

They say that violence is justified if it is a response to violence or a prevention of forthcoming violence. They say that humbleness and cowardice are worse than resistance to violence. At the same time, there is the third possible response to violence by with the exception of violence.

Non-violence is active opposition against violence. It is an attempt at overcoming of unjust situation by non-violence means. Non-violence is different from violence as a realizing of positions of good and evil among people. People simultaneously could be good and evil. Human soul is a field of fighting between its immanent good and evil sides. Even the most virtues people bear some inspired marks of evil and the most of vicious persons have some particles of good in their soul. To consider man as evil is to calumniate about him. At the same time, to account human as good is much to praise for him. Human moral nature is ambivalent however any man may be open to good and collaboration. There is necessity to remember the human moral ambivalence and to organize behavior according to appropriate principles of non-violence.

Firstly, there are a refusal to monopoly of truth, willingness to change and an opening in dialog and compromises. Secondly, everyone should be in readiness for critical attitude towards his behavior. There is often a cause of hostility is hidden in our souls. Thirdly, there is an ability to see a situation in perspective of opponent with purpose to understand him and to find adequate resolution of conflict so he could keep self-respect. Fourthly, it must fight against evil but it should sympathize with persons who are caught in a net of evil. Fifthly, it needs to be open-hearted and to be not cunning in respect of opponent. Thus, non-violence is not submissiveness. There is soon a post-forcible

stage in a historical development of fighting for social justice.

However, it should remember that non-violence demonstrated its effectiveness only in the East (India) where there is a suitable mentality. There is not an actual practice and philosophy of non-violence in the West yet. Situations of totalitarianism also raise many queries about perspectives of possible application of non-violence.

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METHODOLOGICAL UNITY OF SCIENTIFIC PERCEPTION AND HUMANISTIC PHILOSOPHY OF EDUCATION

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Starting with the end of XIX century research workers has been paying more and more attention to the ways and methods of scientific mentality. From that time the intensification of natural science reflectivity, which ended with a revolutionary methodology change and forth – with science paradigms' change, has been observed. Reflection of scientific cognition methods in natural science of XX century manifested and proved itself to be a creative and revolutionary mentality mechanism. From then forward progressive methodology principles of natural science became the foundation of humanistic philosophy of education. Natural science of the first third of XX century became the field of intellectual progress, achievements of which are expected to be developed by the society and other fields of science and education. In philosophy that period is marked with confirmation of unclassical objectivism.

At the same time dehumanization of scientific perception manifested itself. And it resulted in the fact that a research worker, separating himself from the nature fully, observes it from aside, thinking that the nature "doesn't notice" him and behaves as if there is no him at all. But such suspension of perception from reality slowed down the cognitive process. Its further development required attention to the subject of the research. At the beginning of XX century progressive scientific research required from the scientists to include that method, by means of which the cognition is carried out, into the content of cognition. Studying, understanding methods of thinking brought the scientists closer to realizing the fact that knowledge, as well as knowledge got by experimental and theoretical science, contain the properties not only of the reality studied, but also those of the researcher himself.

The modern process of involving methodology into the content of education is associated with apprehension of thinking methods as well. By methodology not only the apprehension of cognitive methods is meant, but also the philosophic understanding of theoretical foundations of science. In this connection there appears the need in methodological reflection. Methodological approach in education turns to be necessary not only as the highest level of theory apprehension, but also as the way of self-cogitation. At present the scientific value of methodology increases. Processes referring to methodological revolution are taking place in science. Recessionary phenomena in educational practice result in the urgency of deep methodological understanding of these phenomena. Enhancement of attention to the methodological educational problems' reflection is becoming an essential condition of education philosophy development.

Science methodology reflection leads to changing paradigms and has a revolutionary, and thus, creative character. Hence it appears that the reflection of methodology presets a humanistic character to the period of scientific paradigms' interchange. If methodology as a science of methods shows the way to knowing the truth, then in humanistic education philosophy methodology sows the way to self-knowing and self-development. Addressing to methodological reflection in science is conditioned by identification of education humanization peculiarities. Humanization of education of a human-being belonging to modern civilization is controlled by the intellect, the defining capability of which at the beginning of XX century became the reflectivity. Methodological reflectivity

represents the highest level of intellectual reflectivity.

Modern science methodology reflectivity is aimed at including a human-being and historically developing society into the subject of its research. Understanding methods and ways of thinking in research, reflectivity enhancement, widening of application sphere of philosophic approaches, are illustrative of the theory of education during the period of a paradigm shift; that witnesses its inner readiness for the paradigm shift.

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ROLE OF FAMILY IN MUSICAL EDUCATION OF A CHILD AS AN OBJECT TO STUDY IN THE SYSTEM OF TRAINING A MUSICIAN-TEACHER (ACCORDING TO DEMANDS OF STATE EDUCATIONAL STANDARD OF HIGHER PEDAGOGICAL EDUCATION)

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According to the demands of State Educational Standard of Higher Pedagogical Education (SESHPE), 2005, maintenance of contact with pupils' parents and rendering them aid in family education is among professional activity routine problems which a graduate of a Higher Institution on speciality 030700 – "Music Education" – should be able to solve. However, the course "Family Pedagogy", unlike other pedagogical specialties, is not provided for the future specialists in the field of Musical Education. The information about a child's education in the family appears to be dispersed among different disciplines of the curriculum. So, in the process of studying philosophy and sociology students get knowledge about a family as a social institution and a small social group; pedagogy – about the specifity of family education and methods of family diagnostics; history of musical education, theory and methods of music teaching – about the role of family environment in musical development of a child. Separate parts of information about family education, cooperation of a musician-teacher and children' parents the students can get in the process of studying general humanitarian, general professional disciplines and disciplines of subject training. The knowledge got is realized by the students in the process of student teaching.

The dispersion of the information among different disciplines of the curriculum results in the fact that the general picture of knowledge of the future musician-teacher about bringing-up a child in the family is mainly more mosaic than integral and doesn't reflect the specifity of the oncoming professional activity sufficiently. The necessity of introducing a classroom discipline of generalizing character which would immediately elucidate problems of family education in the context of musical education of a child is felt urgently.

The actuality of special addressing to family terms of reference in the context of musical education is conditioned by a series of specific features of the defined process. Children's musical education in the Russian Federation is known to be differentiated into basic (compulsory, free of charge, solving problems of general musical development of a child) and complementary (got at will, realized for a fee, solving problems of extended music, and first of all music-instrumental, training). The last, in its turn, is differentiated into music education oriented on a high achievement level and supposing getting professional music-performance or music-pedagogical education, and, so called music education "for one-self", where the student himself determines his pretension level. Under the given conditions the SESHPE about the readiness of the "Music Education" speciality graduates to maintenance of contact with the students' parents and rendering them aid in family bringing-up, acquire manifold substantial interpretation.

Music-pedagogical education of parents, their involving into cooperative with their children musical and artistic activities, rendering consultative aid to the family when choosing directions of complementary musical education of a child are the predominant directions of a musician-teacher in the system of compulsory (obligatory for all) education. In the system of complementary music education the teacher has

to be ready to solve manifold tasks of interaction with thepupils' families. The tasks are conditioned by the specifity of the musical educational process itself, and namely: the early starting of specialized music classes, the cycle duration of studies, high cost of teaching and the necessity of a child's home playing the music instrument. As it stands on the part of the family it is required to determine timely in the system of complementary music education, to provide material and organizational sides of the educational process, to organize personal home micro-environment promoting the success of music education of a child. Management of music-educational process on the part of the family is incarnated in manifold variants of parent-child relations – from optimal to perturbed, demonstrating evident or concealed family ill-being. The stylistics of interfamilial relations in many ways determines the features of the communication of a child and the teacher in conditions of individual music lessons.

According to the requirements of the SESHPE, defining the readiness level of speciality "Music Education" graduates, we elaborated an educational program of the course "Family and the Child's Music Education". General labour intensity of the course is 26 hours, 18 of which are given for auditorium classes (12 lecture and 6 practical ones), and 8 – for solitary students' work. The course is delivered in the 9th semester. It is aimed at the integration of information about family education in the context of actual problems of music education and bringing-up.

In the process of studying the course the following problems are set and solved: to introduce actual problems of music education, the sources and solving reserves of which lie in the field of family education, to students; to make actual students' knowledge about family (and music as well) education, which he got in the previous stages of education, and their life and pedagogical experience; to trace genesis of native family education in the context of children's music education; to understand the significance of music-aesthetic component of family education in its historic retrospect and in modern conditions; to refer modern approaches to family type design practice, conditions of family education, parent-child relations, family roles etc. with the problems and the specifity of the children music education process; realize the got knowledge in conditions of pedagogical modeling.

Students are offered five topics of generalizing character. The topic "Music Education of a Child in the Family in the Context of Cultural and Historical Traditions of the Society" bears a surveying historical character. Special attention is paid to the genesis of native family education and its music educational component. The topic "Educational potential of families of different types and its role in musical development of a child" is devoted to the urgent problem of quality conditions' estimation of children's family education. In the topic "Teaching a child music as a component of educational policy of modern native family" the characteristic of typical parents' positions, conditioning the choice of music-education direction as the prior one, is given on the basis of the surveys carried out by the author. The content of the topic "Parent-child relations in the process of children's having music lessons" provides various samples of parent positions concerning music education (optimal, adequate and non-adequate). Different variants of positive and distorted parent-child relations, which are formed in the process of the child's going in for music, the specifity of development of typical informal roles of the child in the family are analyzed there. In the topic "Peculiarities of interaction of a teacher and families of the children in conditions of basic and complementary music education" modern methodical potential of interaction of a musician-teacher with the children's parents is characterized, and forms and methods of involving the family into cooperative artistic and creative activity are discussed.

The program "Family and the Child's Music Education" is implemented into the academic process of Music and Arts Education Faculty of Ural State Pedagogical University and supplied with the corresponding name educational-methodical complex (monographs, educational-methodical manual).

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PSYCHOLOGICAL FUNDAMENTALS OF FORMATION AND DEVELOPMENT OF VALEOCONATIVE STRATEGIES OF A PERSON IN THE CONTEXT OF HEALTH CREATIVE ACTIVITIES

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Social and economic transformation of modern society generates objective need for preservation and strengthening of individual health of growing up generation, which within the framework of updated system of school education in our country makes actual the problem of formation of pupils' health culture.

Stable motivation on formation of healthy way of life and development of health protective behavioral strategies (valeoconative) of a person is considered today as one of the priority directions of humanization and valeologization (valeology - a science about healthy way of life) of modern education system's strategies mentioned above [1;2].

The realization of these strategies is possible only through formation at subjects of educational process of such base competence, as valeological erudition.

A number of normative documents of the Republic of Kazakhstan (RK), such as the State program of development till 2015, the program "The Youth of Kazakhstan - 2030", the Law of RK "About the state youth policy", the Law "About education", the concept of strategic development of RK till 2030, the Message of President of RK N. Nazarbaev to people of Kazakhstan shows the necessity of designing of educational process for the given aspect.

International Standard ISO 18.00.01 "Safety of ability to live and protection of natural resources" introduced in Kazakhstan, accentuates its attention on modelling and development of health protective educational environment and it states: "Health protection is a priority direction in activity of any advanced state showing care of well-being of people, providing adequate actualization of personal resources in various fields of activity".

Thereupon, it is possible to ascertain, that this very problem has socio-cultural orientation and is a primate of human values at the present stage of society development.

However, the basic mechanisms, stimulating formation of valeological erudition, especially in its methodological and substantial reorientation on education in the sphere of health culture, are not quite enabled in the system of school and high school education existing nowadays. These mechanisms are aimed at formation of stable motivation to healthy way of life and education of a person, who can manage with various valeometrical and health protecting strategies.

In our opinion, valeoconative personal strategies are forms of behaviour and settings of individual aimed at health protection or autodestructive changes of both individual and others' health.

In order to characterize valeoconative personal strategies, we shall start with the motives influencing the process of realization of health protecting strategy of a person. The following motives can be concerned to them:

- need for personal and professional perfection;
- the environment conducts a healthy way of life;
- stimulation of the teachers realizing health protecting strategy of activity;
- knowledge of your own specific features;
- working conditions make it possible to realize the strategy;
- fear to be ill or case of illness;
- a high degree of responsibility for your health;
- criticism on the part of colleagues or administration;
- lack of material opportunities for maintenance of strategy.

On the basis of the specified motives, we determined some base valeoconative strategies of person (VCSP) and discovered correlation between health protecting strategies and valeological settings.

As indicated in picture 1, among the teachers carrying out educational process in high schools of Shymkent city valeodestructive (undermining one's health) strategies of a person dominate. As for health protecting and health creative strategies, they average only 20% of respondents' answers.

In total, we investigated 600 teachers of comprehensive schools of Shymkent city and 300 teachers of high schools of Southern region.

To conduct the research of valeoconative personal strategies of the teachers we used V. Garbuzov's questionnaire [3]. This questionnaire is aimed at defining the type of dominating instinct of a person.

It is necessary to mark, that, knowing the type of dominating instinct, it is possible to define the type of valeological setting of a person. In its' turn, knowing the type of valeological setting it is possible to reveal some basic valeoconative person's strategies. The logic-structural sequence of the mentioned transitions is shown in picture 1.

Besides, in the context of the given research, our own questionnaire was applied, defining the set of the motives influencing the realization of health protecting strategy. In this very questionnaire, the questions were focused in a special way so that during the process of empirical data we could carry out assessment of inhibitory factors or factors initiating formation of valeoconative strategies of teachers.

Among these factors (by results of interrogation of teachers), the following basic groups were deduced: social and economic; substantial; stimulating; psychological.

Considering, that in these four valeoconative strategies an essential role is played by psychological factor (see picture 1), we think, that only motivation for health protection can be determining criterion of VCSP.

Thereupon, the basic motive influencing the realization of health protecting strategy is the motive of self-actualization. This motive becomes apparent in realization of the purposes, abilities, in aspiration of a person to self-embodiment, to actualization of incorporated potentialities, in self-expression - in full use of the opportunities, achievement of the purposes, in personal development.

Thus, this very motive can provide formation of stable valeoconative strategies of a person.

Experience shows, that the major component of VCSP is such phenomenon, as "culture of health".

Theoretical and experimental researches of the given phenomenon proved, that both in theory, and in practice of vocational training it is investigated nowadays in an insufficient degree.

Interest of scientists to person's culture of health is caused by the changes occurring in social and educational spheres, which are connected with high-grade use of social institutes in maintenance of health, quality of life and education of "the person of culture".

On the basis of the analysis of medical and biological, psycho-pedagogical, philosophical, sociological literature we determined the structure of health culture (picture 2).

It is necessary to mark, that before the experiment we determined the initial health culture parameter of students of the experimental and control groups training at our university on speciality 0314 - "Pedagogics and psychology". The named parameter was revealed at the beginning of the 1st year of studying (2003/2004). Then the intermediate health culture parameter of students of the same groups was defined at the end of the 1st course (2004/2005). We got the results after approving in this experimental group a new integrative course of our own "the Fundamentals of valeology"

The given course was developed by A.Madzhuga (candidate of pedagogical science, reader, the head of chair of psychology at Southern-Kazakhstan State University).

In the given course, working the maintenance of valeological aspects out was provided on theoretical modules.

Each module included the certain spectrum of knowledge necessary for formation of valeologically-oriented person. In contrast to current operating on the territory of the Republic of Kazakhstan programs on valeology for students of high schools, this very course is aimed at acquaintance of students not with separately taken directions on formation of HWL (healthy way of life), but with complex of knowledge providing mastering medical and biological bases of healthy way of life and principles of formation of health culture on the basis of VCSP.

The purpose of teaching the course consisted in acquaintance of students with theory and practice of formation, preservation and improvement of person 's health, and with basic health protecting technologies and means. ,- The course mentioned above included 10 module.

According to the name of each module we can state about presence of integrative components in all of them, i.e. their studying is possible with the help of teachers of the chairs having adjacent specificity with valeological knowledge. Besides, the suggested modules can be modified taking into account the direction of students' training on profile disciplines for certain specialities. That is why, the realization of maintenance of modules (1,2,3) is possible with the help of teachers of chairs of biology and physiology, chair of geography, module 4 - with the help of teachers of chairs of biology and physiology, module 10 - teachers of chair of philosophy, pedagogics and valeology.

Alongside with theoretical aspects of valeology, in the program of the course the list of laboratory researches which maintenance is also directed on formation of valeologically-oriented person is resulted.

It is necessary to mark, that in the course program the attempts to reveal valeological knowledge in social-biological, social and economic, medical, ecological, philosophical, psycho-pedagogical aspects are undertaken in Kazakhstan for the first time, i.e. formation of students' culture of health has implicit character.

In our opinion, such logical-composite structure of the course, makes it possible to create strong methodological basis of valeological knowledge of students, to generate their health culture, to define one of the main criteria of readiness of intending teacher to professional work.

After taking the course "The fundamentals of valeology", the students of experimental groups during all the period of training in High school were in the constant process of formation of valeological settings having self-sufficient (resource) character, i.e. the student was focused on independent maintenance of health and following healthy way of life.

It is our opinion, that this phenomenon is concerned with formation of student's steady valeological consciousness and actualization of zones of "person's common sense". That is why we can speak about motivation on health itself and healthy way of life, and health is admitted as lasting value.

The analysis of integrated assessment of health culture of students of experimental and control groups testifies that the number of students who reached a high level of development (creative) of valeological culture, is higher in experimental groups with expanded complex of psycho-pedagogical conditions (teaching of the course "the fundamentals of valeology"); allowable and insufficient - in groups with traditional organization of educational process. The percentage of the students possessing the given quality is presented in table 1.

Thus, in the context of modern fundamental changes occuring in society, our main aim is to form students' need in health as vital value, conscious aspiration to healthy way of life, to "self-creation" and creation of healthy environment -formation of valeological culture of a person as part of its general culture.

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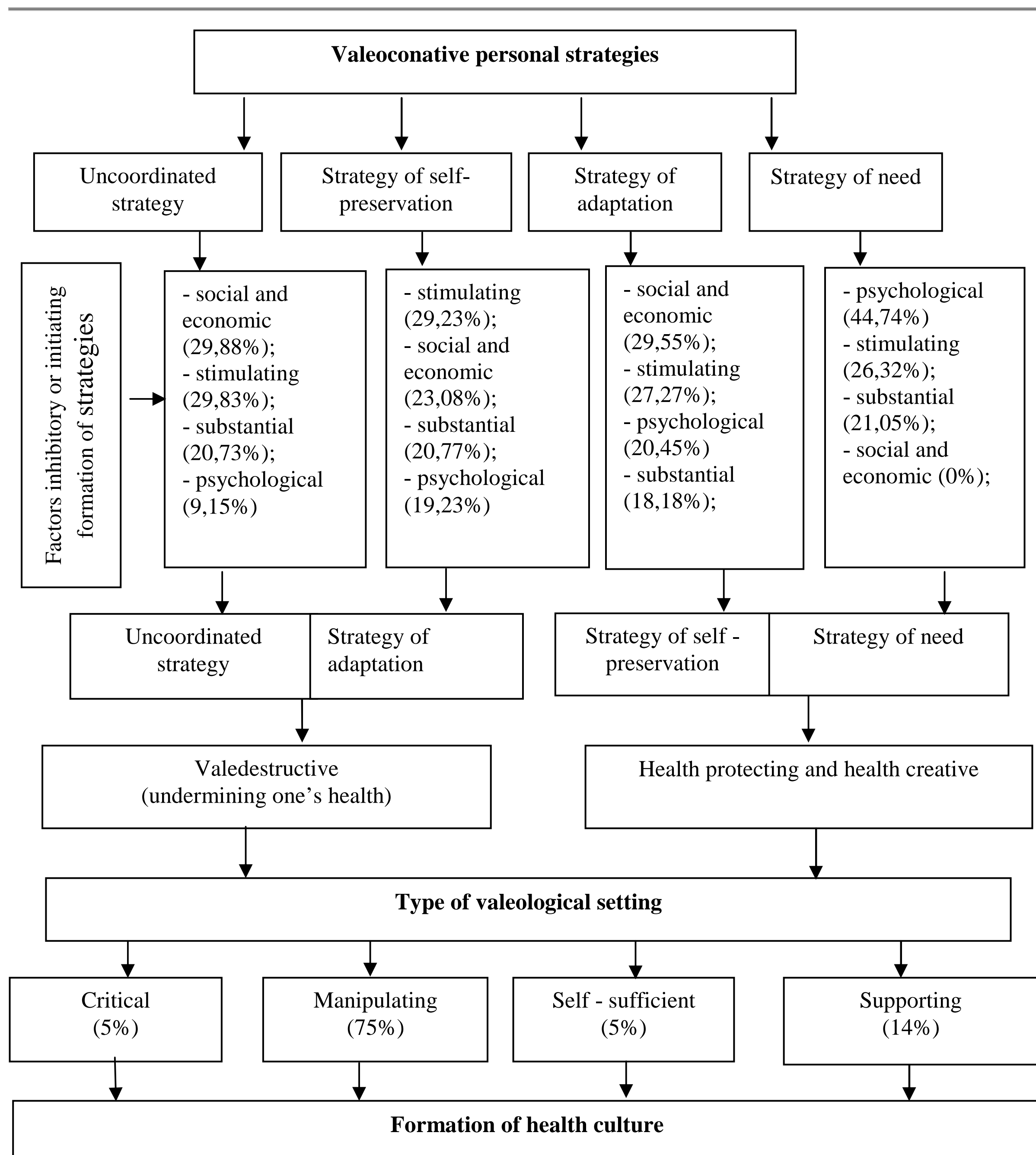
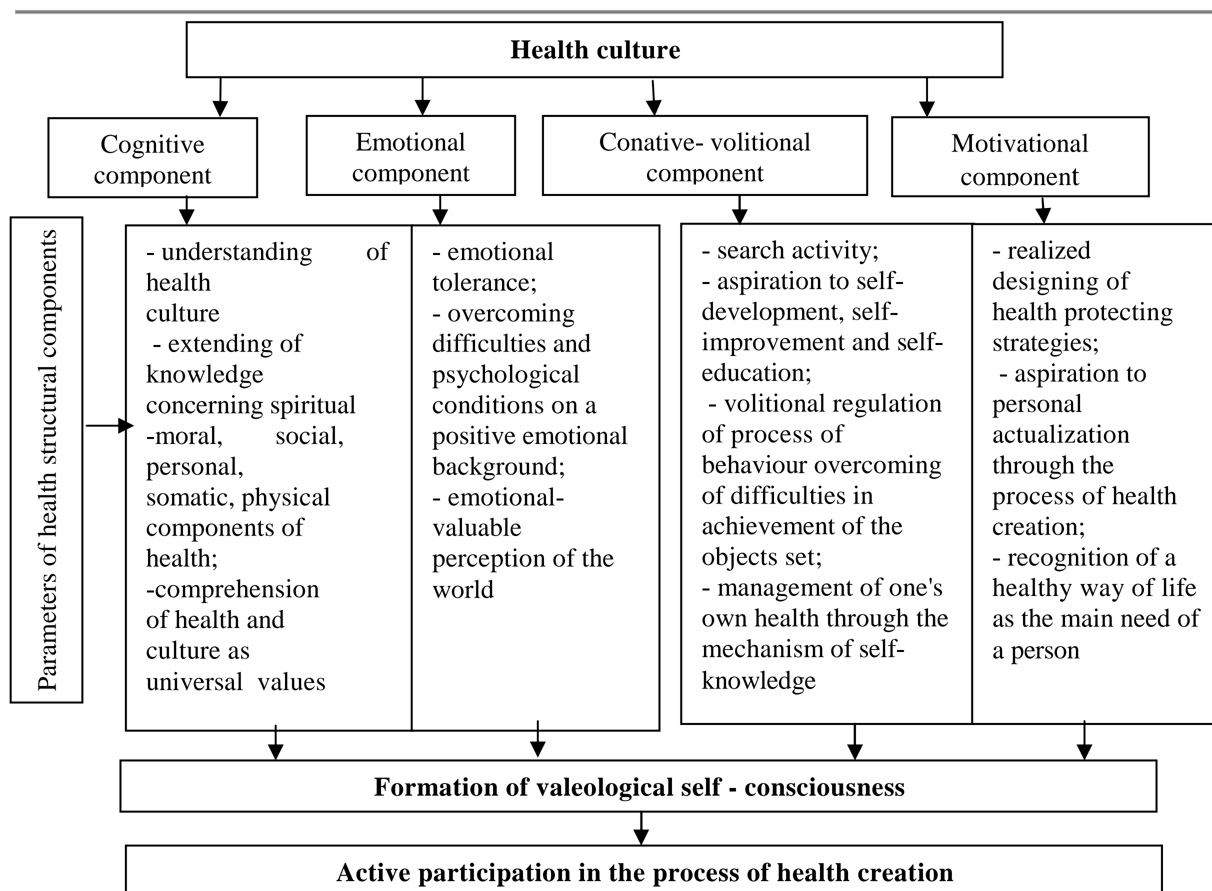
Table 1. The percentage of examinees according to their level of health culture development at the end of research (%)

Level of valeological culture	Integrated multifactorial assessment of the level of development of valeological culture (% to the total number of students)											
	1-st year				3-rd year				Final year			
	Control group (2000-2001)		Experimental group (2000-2001)		Control group (2001-2002)		Experimental group (2001-2002)		Control group (2003-2004)		Experimental group (2003-2004)	
	beg. of year	end of year	beg. of year	end of year	beg. of yea	end of year	beg. of yea	end of year	beg. of year	end of year	beg. of year	end of year
High level	5.5	6.9	4	10.7	6.9	6.9	0.7	0.7	8.2	9.6	29.3	1.3
Sufficient level	7.8	575	8.7	2.7	5.2	61.6	58.7	54.6	52.1	54.8	57.3	52.0
Allowable level	76.7	36.6	77.3	26.7	47.9	31.5	30.7	14.7	39.7	35.6	13.4	6.7



Picture 1- Designing of valeoconative strategies of a person



Picture2 - Structure of health culture

THE EXISTENTIAL-HUMANISTIC APPROACH TO FORMATION OF PERSON'S INDIVIDUAL VALEOLOGICAL CULTURES IN THE INNOVATIVE ENVIRONMENT

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The problem of preservation and purposeful formation of children and youth health is exclusively significant and actual in difficult modern conditions of Kazakhstan development, because it is connected with a problem of safety and independence.

Last year in Kazakhstan there was a significant qualitative deterioration of schoolchildren health. According to some researches, only 10 % of school graduates can be considered healthy, 40 % have various chronic pathology. Each second schoolboy has the combination of several chronic diseases.

While studying at school the number of children with infringements of the support-impellent device increases in 1,5 - 2 times, nervous illnesses - in 2 times, with allergic illnesses - in 2 times, with short-sightedness - in 3 times.

Especially negative situation with pupils' health is marked at schools of new type (grammar school, colleges, licea, schools with the profound studying of subjects, etc.). Educational process there is characterized by the raised intensity. By the end of a school year at grammar-school boys frequency of hypertonic reactions increases in 2 times, and the common number of adverse changes of arterial pressure reaches 90 %, raised neurosis displays. It is

marked at 45 % - 75 % of pupils of schools of new type.

Experience shows that one of the priority directions in complete health studying is the questions of technics and technology of healthpreserving educational space formation.

The term «healthpreserving educational technologies» can be considered as the qualitative characteristic of any educational technology, it is «the certificate of health safety», and as a set of principles, receptions, methods of pedagogical work. They give supplementing traditional technologies of training and education the mark of healthpreserving. Within the limits of healthpreserving problem there are two basic approaches - medical and psychological.

The medical approach to healthpreserving, sold within the limits of a preventive direction, differs from psychology-pedagogical not only in methods and vocational training of experts, but It also relieves from person's responsibility for his health and transmit this responsibility to the doctor and medicine. The psychological approach consists of mobilization of responsibility of a person for his health, education of constant need to care of it (so and about health of other people).

Today qualitatively new approaches to the decision of the question of nation health preservation are necessary without ignoring the best things that are already turned out in the field of the prevention and treatment of various illnesses. We consider that novelty of approaches should follow from the necessity of a person to care about his own health, interest and activity in healthpreserving and healthbuilding. It demands, first of all, new thinking, to be exact - new consciousness, that is reorganization of sights at a problem of the person's health.

Being one of intrinsic characteristics of the person, his health defines a degree of viability, stability of an organism, an opportunity to realize the biological and social functions. In this connection solving a problem of preservation and strengthening of person's health the major accent is given to a problem of health formation as sufficient level for successful ability to live.

Thus, there is a question on development and education healthdirected orientation of a person, his attitude to health as to the supreme spiritual, mental and physical value during realization of the scientifically-proved social and economic, medical and biologic, ecological, psychology-pedagogical measures directed on increasing person's life activity in changing conditions of environment.

Within the limits of our research we tried to define the maintenance, structure, the basic connections of the phenomenon of «healthdirected orientation of the person». As a result of the analysis of the philosophical, psychological, pedagogical sources we have come to the following.

In psychology the orientation of a person is considered as a set of the steady motives that focus person's activity in independent situations. The orientation of a person is characterized by his interests, installations, belief, and ideals, valuable orientations in which the outlook of the person is expressed.

Healthdirected orientation of a person is closely connected with valeological (healthdirected) consciousness, and valeological thinking.

His motivational-valuable character, ability to reflect, introspect, to make an internal dialogue that directly defines person's outlook and orientation, characterizes the consciousness of a person.

Healthdirected consciousness is wider, than valeological thinking. Healthdirected orientation of a person includes intellectual, strong-willed, emotional-sensual and motivational components.

The intellectual component essentially influences depth, completeness, creative character and productivity of valeological activity, in many respects defining shape world outlook installations of the person, so also his orientation on healthpreserving and healthincreasing processes.

The motivational component is expressed in a need to carry out a task successfully, interest to object of an activity, ways of its realization, aspiration to success, professional-significant needs, motives of pedagogical activity, the positive attitude to profession , an interest to it and other steady enough professional motives.

Strong-willed component includes self-checking, skill to operate actions that form a performance of duties, characterizes the internal need to operate actions, assumes a self-estimation of the readiness and conformity of professional problems decision process to the put samples.

Emotional-sensual component characterizes feeling of the responsibility for pedagogical activity results, self-checking, skills to operate actions that form a performance of duties.

Functions of healthdirected orientations of a person are target designation, diagnostics, prediction, forecasting, free choice of purpose achievement variants, estimation of the received results. Functions of the valeological thinking: problems solving directed on preservation and strengthening of health, output from the situations menacing to person's health.

Subject of action of person's healthdirected orientation is healthpreserving and healthcreating processes, valeological activity. Subjects of the valeological thinking are valeological actions, situations, and events.

Healthdirected person's orientation it is closely connected with valeological culture (culture of the person's health).

So important component of health culture as valeological outlook represents the specific form of consciousness of a person. Researchers find here a system of valeological knowledge, sights, belief and ideals. There is person's attitude to development, preservation and strengthening of his health, health of surrounding people and environment in them.

Besides healthdirected person's orientation is closely connected with healthcreating behavior. T.Orekhova defines it as the behavior allowing a person to live in harmony and consent with surrounding people and world. That is the behavior when actions of a person are structural units, elements of his ability to live, provide preservation, maintenance, strengthening and escalating of person's health and surrounding people as well.

If healthdirected person's orientation carries out, basically, world outlook function in becoming person healthcreating behavior carries out, in a greater measure, regulatory function, that it provides regulation of its activity.

«Healthdirected person's orientation» is a set of dominating motives, valuable orientations, significant interests, installations and attitudes of a young man as concept, focusing him on constant conscious realization of healthsaving and healthcreating activity.

On the basis of the given representations we have developed the model of structural elements of the information-educational orientation making a conceptual basis of the pupils valeological education.

The model consists of rod blocks of humanistic education, algorithms of decisions, an orientation of actions (vector of administrative decision) and valeological-educational vector of healthcreating (see Figure 1).

Last becomes isolated on a vector of the valeological-improving means, methods and technologies and on a vector of administrative decisions accordingly. Thus vectors are shown as fragments of the monitoring approach using plan of the healthsaving environments of pupils. In this model of the levels there are fragments of a theoretical and conceptual basis of pupils physical training. This block of model becomes isolated on perspective-forming prognostic stage.

The vector of administrative decisions finds its continuation in preparation and formation of the decisions that have expressed in object, subject, purpose and hypothesis of researches. Block of the scheme of exploring-alternative applied decisions and general educational orientation in valeological-educational vector of pupils healthbuilding finds its continuation in making problem situations and selection of means, and also in formation of the purpose and alternative of a decisions choice.

The choice of the decision in a vector of administrative algorithms of the block of base developing educational orientation closely coordinates with the idea of formation of criterion and a choice of optimum decisions of all course and reasoning in the offer of alternatives.

Realization of decisions in a vector of administrative operations finds refraction and logic end in blocks of the scheme ecological-pedagogical educational orientation and the monitoring of healthbuilding, corrections and the control of the valeological education and pupils' motivations. It is carried out in two stages.

The stage of acquaintance with the bases of knowledge, skills, bases of healthcreating with elements of a pedagogical educational orientation is built during monitoring valeological education. While studing pupils get acquainted with elements of knowledge on bases of a condition of the health and skills of diagnostics.

With the use of the comparative analysis that, in its turn, enables with high degree of persuasiveness and presentation to construct and

estimate an individual anthopometrical structure of a pupil, the logic of tactics is built where it is made a correction of the training program of lagging behind or underdeveloped morphometrical facts. It is carried out the strategy of operated decisions in a choice of an optimum variant in realization of healthbuilding decision on immediate prospects.

The model of modern educational process is based on physiological and physiology-pedagogical preconditions of optimality and gradualness, use of functionalities and health level of a young organism. The offered model of the management scheme and algorithm of the healthsaving allows to carry out substantial-remedial use of a healthcreating valeological-educational vector of a growing organism of a child through procedure of pedagogical technologies and administrative decisions.

In healthsaving structure of an educational institution it is possible to allocate spaces of phenomenologically close phenomena. Figuratively it can be presented as a sphere of several different colors. Each of them defines a set of phenomena, as a component of the sphere. These sets of homogeneous phenomena, "subspaces" we name ecological, emotional-behavioural, verbal, culturelogical etc).

At present there are two basic approaches to formation of health in the educational environment.

1. Healthbuilding is based on following certain models of preservation and formation of a healthy way of young people life. It includes healthsaving behaviour designing. Healthbuilding includes the majority of healthsaving programs applied in educational institutions. Using the given techniques the greater attention is given to practical methods of healthsaving environments creation. Pupils act in a role of healthsaving objects in this case.

2. Healthcreating is based on involving of an individual in the process of health creation, prompting aspiration to perfection of health preservation forms. It includes an increment of healthbuilding resources to creative component in the existential attitude to the health. At the given approach pupils are not only objects, but also healthsaving subjects. In this case the understanding of healthsaving problems occurs much more deeply. And if in the first case pupils can neglect opportunities of health preservation because of their spirit of nihilism that is peculiar to youth, in the second case, being involved in the process of health creation, they are more responsible to the given problem. If pupils are not given the ready technique, their actions are directed on formation of their own technique from already known and accessible technical healthsaving means at the initial stage. The achieved effect will be considerably above than that in the healthbuilding approach.

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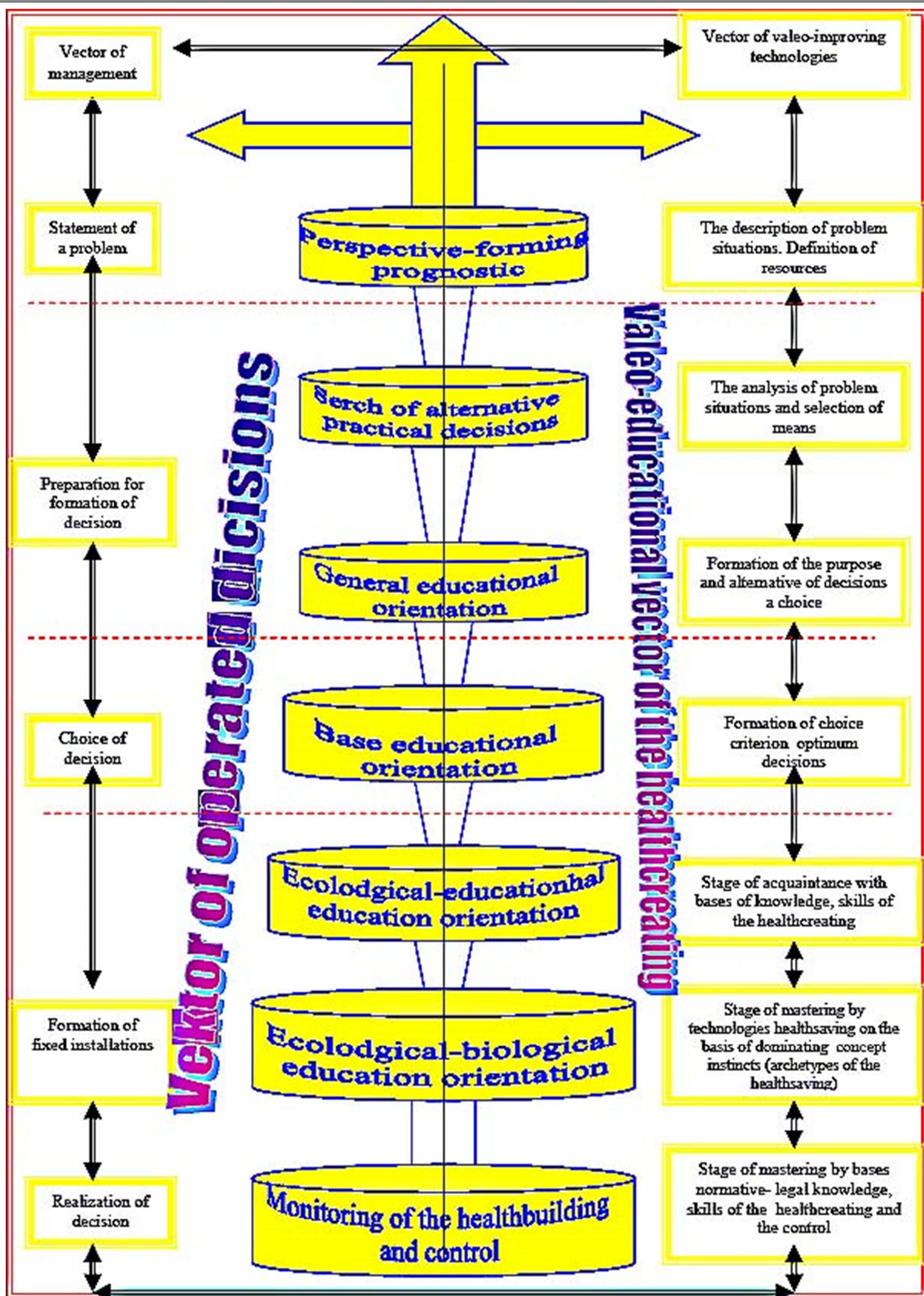

Figure 1. Vector-level Model formation healthdirected orientations of the person
Data on authors

Shot report

TRANSFORMATION OF WELFARE STATE FUNCTIONS IN THE TRANSCENDENCE PERIOD TO ANTHROPOCENTRIC DEVELOPMENT MODEL

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Developed modern countries identify themselves as "welfare states". The definitions of a welfare state, having been formulated within the period of more then a hundred years, beginning with Lorenzo von Stein (1850 г), underwent radical changes [1], as the state itself had been suffering from evolutionary alterations reflecting productive forces and public relation development [2].

The dynamics of principal concepts, their content and characteristic features of a welfare state generalized by Kalashnikov S.V. [3] look like the following:

1. Primary welfare state (80-s of the 19th c. – 30-s of the 20th c.): the citizens have got social rights, and the state – social responsibility. Features: all-round introduction of social insurance, provision of social equality, budgetary financing of national social aid and separate social programs. The state becomes a predominant subject of citizens' social assistance (communities, cooperative societies, church, and charity).

2. Legal welfare state (30-40-s of the 20th c.): system of civil rights to social protection on the part of the state. Features: social functions of the state not just acquired legal foundations, but became leading for nations. Personal human rights became a foundational part of the whole state legal system, determining social duties of the state through the civil rights.

3. State of welfare services (40-60-s of the 20th c.): the state is a subject of specific social functions - employment provision, formation of life medium for invalids, etc. Features: the state is responsible for equality of opportunities for all social groups of the society on the ground of active social policy. The state not only compensates impossibility of a person's achieving certain life standards, but actively forms the conditions of their achieving. The state is the guarantee of equal social opportunities.

4. State of universal prosperity (60-80-s of the 20th c.): achieving of relatively equal high life level of the whole population. Features: period of maximal development of insurance signs and giving the principle of solidarity priority number one. It determines the generality of social assistance, orientation on universal quality of life indicants, mechanisms of social risk insurance preferentially on solidarity foundation.

5. Universal prosperity state crisis (80-90-s of the 20th c.): growing gap between the number of social contribution payers and those who are entitled to social security services: the unemployed, poor, single-parent families, etc. Features: crisis of the entire solidarity insurance system. Contradiction between growing social allocations and objective necessity of tax deduction on business.

6. Liberal welfare state (middle of 90-s of the 20th c.-present time): social policy efficiency. Features: divestment from paternalistic state role and political objectives to life leveling of citizens. Sources and pre-conditions of liberal welfare state becoming are discussed in the clause.

New state functions in the form of national insurance, creating and budgetary financing of national social assistance and separate social programs, provision of equal access of all citizens to client care plan, became real. Compared to preceding period the state became a predominant social function subject in the society, and earlier theses functions were carried out by market subjects (charities) – church, communities and other forms of collective human activity, cooperatives, for example [4].

Welfare state legal reasoning perfected the principle of natural social human rights. The state became an intermediate link between human rights collection and the society, and on the ground of social policy started providing these social rights. In this quality it received specific

rights to secondary distribution of goods and so acquired a specific *function to guarantee initial, starting opportunities of the citizens.*

A modern welfare state claims maintenance of the balance between freedom and equality; the equality being dynamic and not static one. The state should provide a citizen not only with freedom but real opportunities to use it. The problem of opportunities is the corner stone of the argument: to provide equal life conditions and equal life chances. Before the 80-s in science research and state policies of many European countries the priority of the first equality form dominated. At present the majority of scientists abandon themselves to the idea that social justice should be founded on economic liberalism: a state should be responsible for life and labour conditions of its citizens having social rights. The citizens' rights consist in realization of economically and socially acceptable life level for all and in providing them with equal life chances (education, health care, culture).

A modern welfare state, in our opinion, should be understood as a dynamic economical system, in which the social protection foundation is successfully developing market economics itself, complemented only the most necessary measures on the part of the state. A liberal welfare state starts having new, earlier neglected by it, functions (Table 1), which are the reaction on alterations of social-economic conditions, wherein the modern state develops.

Rights and responsibilities asymmetry compensation pays great attention to the national insurance principle which establishes benefit sizes in proportion to contributions to the system (priority of the insurance principle over the one of social assistance). It is necessary for the removal of contradiction between rates of economic growth (assessment severity and employers' social benefit values) and the level of provision assistance to the population in case of occurrence of hazardous situations.

We consider that the main vector of modern economic development is the transcendence from technogenic type of production to innovation-information economic system, when social production factors turn into the main source and impulse of economic development, when the employee cannot be seen only as a means of economic effect maximizing.

High-tech production ruined the ideas of unprofitability of social expenditures slowing down accumulating, expansion of production and its competitiveness. In an industrial production, especially on the primary stage which is characterized with an expansive character, developing on the account of earned value the economic efficiency directly depends on simple, intensive labour. For such a production the opposition of economic and social priorities is typical of: the last are restricted with the necessity of simple reproduction of labour-power. There is no need of other investitures, as a matter of principle, and once got qualification can be used in the industrial production without sufficient changes for 20-30 years.

Under the conditions of continuous perfection of productive powers the investments to the man become objectively necessary as not a simple labour, and not even a complex one being thought as mechanically multiplied simple labour is required already, but a labour associated with continuous knowledge renewal, capability to think analytically and react the requirements of the production competitiveness growth. There appears a feedback effect: postindustrial production creates preconditions for "socialization" of economics, but at the same time it is a precondition for organization, deepening and development of modern innovation-information economy.

The emerging role of social context in modern innovation-information economy allows many scientists to consider such an economy to be anthropocentric one as the role of material factors becomes more and more mediated, dependent on organically included in national economy structure of organizational, technical and scientific creativity. It goes without saying that what is meant here is a technologically advanced postindustrial economy.

That is why the strategy of modern economic system development in a postindustrial society as one of the four internal factors considers "developing human capital by means of investments to education, health care, culture, housing improvement, staff training in accord with prospective demand on the labour market and possibilities to compete on the labour market" [5].

Table 1 – Signs and social functions of a modern state

Signs	Functions (in order of their appearance)	New functions of a liberal welfare state under the conditions of industrial- innovation economy
National social assistance availability for all society members Legal nature of social policy – the right to handle and control Budget welfare benefit system availability Social safety net availability (including systems of population employment and welfare) Recognition of the state responsibility for the welfare level of its citizens Civil society institutions' availability	Social welfare Available health care (social insurance) Social protection Social services' available Employment provision Leveling of social inequality Carrying out national social policy	Rights and responsibilities asymmetry compensation Removal of antagonism between social objectives and market requirements Guarantee of achieving high economic indicators and competitiveness of the county on account of social factors Protection against social non-insurance hazards on account of effective economy on the ground of damage compensation principle

*Is made by the author

Potential for development of modern economical systems is measured by the indices of human development and innovation-investment activity which are the key factors of postindustrial economy development.

Thus, modern economic systems are specified by societal development economic and social context balance alteration in favour of the last one. Acquisition by them the role of economic growth basic impulse has got a double nature. On the one part it is the result of science-technical progress and welfare state evolution, and on the other part – features of human potential (education, health, culture level), they being a precondition for the development of new quality economy, innovation-information one. In connection with this a welfare state has modified its functions having added to existing ones the function of guaranteeing of achieving high economic indicators and competitiveness of the county on account of social factors.

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Shot report

STUDING OF THE PERSON OF THE DOMESTIC BALLET MASTER IN CULTURAL SCIENCE

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Creativity of known modern choreographer D.A. Brjantsev deserves attentive studying.

Being the main ballet master of the Moscow Musical theatre of a name K.S. Stanislavsky and V.I. Nemirovich-Danchenco, D.A. Brjantsev has put popular teleballets "Galatea" and « the Old tango », and also performances - « the Hussar ballad », "Humped horse", «Nine tangoes and … Bah » and many others on stages of theatres of Moscow, Leningrad - Peterburg and Krasnodar. Any themes and genres, the form of multievent performance and ballet miniatures, the most various choreographic lexicon are subject to D.A. Brjantsev: classical dance and free plastic, dance household and variety.

One of the bright ballets put by D.A. Brjantsev, began ballet « the Illusive ball » on F.Shopen's music (on his nocturnes, mazourkas and the second part of the Second concert for a piano with an orchestra). « Illusive ball » strikingly it is not similar to one of the previous ballets. The choreographer has refused a plot to which always gravitated, from dynamics of development of action, from precisely drawn dramatic art, from logic correctness of events, from a bright portrayal of characters of characters. His ballet as if is weaved from visions and presentiments, from easy sighes and silent pauses, from the escaping memoirs which have revived behind a veil not of procast tears …

The ballet composed on the end of XX, sends us to his beginning. Associations with Petersburg here persistently are prompted not only stylisticaly D.A. Brjantsev's with faultless lexicon, but also all atmosphere of performance, his laconic - strict registration executed by artist V. Arefjev. What it - « winter dreams » about Petersburg seen through a Mirage of a snowfall in silvery light of the moon, or transparent haze the "thoughtful" white nights which are fancifully washing away borders between dream and reality?... Feelings of heroes are deeply latent. Entreaty, a recognition, oathes are designated by executors only hints - in fleeting embraces, in whisper of silent run, in hardly appreciable sights usually looking down eyes. Language of classical dance is combined here with difficult supports, masterly lexicon of modern dance. But these free « infringements of rules » are not perceived by a stylistic discord as are subordinated to the general choreographic figure, uniform hardly to a delayed rhythm.

Dancers of the Moscow Musical theatre appeared sensitive to D.A. Brjantsev's choreography, the blessing grew and were formed on his ballets. Correctly having felt originality of lexicon of D.A. Brjantsev, they have highlighted set of the most interesting plastic nuances, theatrical individualized heroes, having made everyone blows an independent short story about love - about not holding, lost or and not found happiness.

« Illusive ball » D.A. Brjantsev has adequately risen in one line with performances which are considered as indisputable masterpieces. On a share « Illusive ball » the extraordinary spectator success and record number of enthusiastic reviews has dropped out.

To write about the ballet master, whose heritage became property of a history, to some extent easier, than about the choreographer modern: the time distance and completeness of a creative way help to place all necessary accents correctly. And for the modern choreographer mutually exclusive judgements about his ballets are pulled different estimations and sometimes. Objective to be difficult, since you are the direct witness of creative process.

The person of the choreographer, the ballet master, the ballet dancer always finds the reflection in ballet performance. And the more interestingly the person, the more considerable ballet statement.