DO LOW DOES OF IONIZING RADIATION AFFECT THE HUMAN BRAIN?

K. Loganovsky

Dept of Radiation Psychoneurology, Institute for Clinical Radiology, State Institution “Research Centre for Radiation Medicine of Academy of Medical Sciences of Ukraine”, 53 Melnikov Str., Kyiv, 04050, Ukraine
Email: loganovsky@windowslive.com

ABSTRACT

The aim of this paper is to analyze the current evidence on radiocerebral effects following exposure to <5 Sv. Dose-related cognitive and neurophysiological abnormalities among prenatally exposed children after the Chernobyl accident at gestation ages of +8 weeks were revealed at >20 mSv on the fetus and >300 mSv on the thyroid in utero; at 16–25 weeks, abnormalities were >10 mSv and >200 mSv, respectively. In adults, radiation-associated cerebrovascular effects were obtained at >0.15-0.25 Sv. Dose-related neuropsychiatric, neurophysiological, neuropsychological, and neuroimaging abnormalities following exposure to >0.3 Sv and neurophysiological and neuroimaging radiation markers at doses >1 Sv were revealed. Studies on radiation neuropsychiatric effects should be undertaken.

Keywords: Ionizing radiation, Low doses, Chernobyl accident, Brain, Radiosensitivity, Radiocerebral effects, Exposure in utero

1 INTRODUCTION

The current challenges of modern radiobiology and radiation protection, which include radiation accidents at nuclear reactors, radiological terrorist attacks using a radiation dispersal device (RDD), the so-called “dirty bomb”, and radiation exposure during space flights, present two very important issues. The first is whether low doses of ionizing radiation have any harmful influence on human health at all, and the second is the acute and still open for more than a century discussion of the radiosensitivity/radioresistance of the brain. These two issues taken together, whether low doses of ionizing radiation affect the human brain, present an extremely contradictory problem. An accidental exposure is obviously associated with: 1) non-radiation factors, mainly, psychological stress, and 2) an absence of the base-line (before exposure) health data of victims. That is why distinguishing potential low doses effects on the human brain is quite a difficult scientific task.

According to the classical foundation of cancer radiotherapy by French radiobiologists Bergonie and Tribondeau (1906), “The sensitivity of cells to irradiation is in direct proportion to their reproductive activity and inversely proportional to their degree of differentiation”. Consequently, the adult nervous tissue was recognized as an excellent example of a “closed static population”, and, because of its fixed postmitotic state, this activity was considered to be “extremely radioresistant”. At the same time, the evidence is dramatically increasing in support of the radiosensitivity of the Central Nervous System CNS (Nyagu & Loganovsky, 1998; Wong & Van der Kogel, 2004; Gourmelon, Marquette, Agay, Mathieu, & Clarencon, 2005). The development and validation of biological markers of ionizing radiation is the primary goal of current radiobiology and radiation protection (Bebeshko, Bazyka, & Loganovsky, 2004).

Recently, reports about the beneficial health effects of low doses of radiation, as a “radio-adaptive response”, were widely published (Chen, Luan, Shieh, Chen, Kung, Soong et al., 2006; Cuttler, 2007; Rodgers & Holmes, 2008). The most conservative threshold of radiation-induced neuroanatomic changes was assumed to be 2–4 Sv for whole body irradiation, while that for the CNS was assumed to be 50-100 Gy (Gus’kova & Shakirova, 1989; Gus’kova, 2007). The radiotherapeutic tolerant dose for the brain was assumed to be 55–65 Gy, and the tolerant fractional dose was assumed to be 2 Gy (Mettler & Upton, 1995). Moreover, a “glial-vascular union” was considered to be the cerebral basis of a postradiation brain damage, while neurons themselves seemed to be out of this pathogenesis: consequently, the brain white matter was considered to be much more radiovulnerable than the brain grey matter. However, the latest advances in understanding the mechanisms of CNS radiation damage demand a reassessment of these assumptions. It is now recognized that the CNS is a major dose-limiting organ in clinical radiotherapy (Wong & Van der Kogel, 2004), and the CNS is a radiosensitive system (Gourmelon, Marquette, Agay, Mathieu, & Clarencon, 2005). The analysis of our own studies in combination with the current evidence on CNS effects of exposure to ionizing radiation in humans in doses up 5 Sv is presented in this paper.
2 RADIOCEREBRAL EFFECTS AT DIFFERENT EXPOSURES SCENARIOS

2.1 Current views on low doses radiation brain injury pathogenesis

Radiation exposure has multiple effects on the brain, behavior, and cognitive functions. These changes depend largely on the dose received. It is well known that ionizing radiation influences CNS functions and behavior both as a result of direct effects on the nervous system and indirectly through CNS reactivity to the radiation damage of other systems (Kimeldorf & Hunt, 1965; Mickley, 1987). Alteration in CNS functioning is likely to occur after relatively low doses of radiation. There is now an increasing body of data indicating that the response of the CNS after irradiation is a continuous and interacting process. Specifically, the focus is on apoptotic cell death and cell death and injury mediated by secondary damage (Wong & Van der Kogel, 2004). Today, it is established that the CNS is a radiosensitive organ whose degree of dysfunction can be quantified by electrophysiological, biochemical, and/or behavioral parameters. Abnormalities in CNS function defined by these parameters may occur at a low dose of whole body radiation (Gourmelon, Marquette, Agay, Mathieu, & Clarencon, 2005).

A recent study illustrated that sub-chronic exposure with post-accidental (Chernobyl) doses of $^{137}$Cs lead to molecular modifications of pro- and anti-inflammatory cytokines and NO-ergic pathways in the brain. This neuro-inflammatory response could contribute to the electrophysiological and biochemical alterations observed after chronic exposure to $^{137}$Cs (Lestaevel, Grandcolas, Paquet, Voisin, Aigueperse, & Gourmelon, 2008).

Brain irradiation modulated the expression patterns of 1574 genes, of which 855 showed more than 1.5-fold variation. About 30% of genes showed dose-dependent variations, including genes exclusively affected by 0.1 Gy. About 60% of genes showed time-dependent variation with more genes affected at 30 minutes than at 4 hours. Early changes involved signal transduction, ion regulation, and synaptic signaling. Later changes involved metabolic functions including myelin and protein synthesis. Low-dose radiation also modulated the expression of genes involved in stress response, cell-cycle control, and DNA synthesis/repair. Doses of 0.1 Gy induced changes in gene expression that were qualitatively different from those at 2 Gy. The findings suggest that low-dose irradiation of the brain induces the expression of genes involved in protective and reparative functions while down-modulating genes involved in neural signaling activity (Yin, Nelson, Coleman, Peterson, & Wyrobek, 2003). Changes in the gene profile in the brain after irradiation are complex and are dependent on time and dose, and genes with diverse functions and pathways are modulated (Mahmoud-Ahmed, Atkinson, & Wong, 2006).

Neurogenesis in the adult hippocampus, which occurs constitutively, is vulnerable to ionizing radiation. Radiation cognitive impairments may involve injury to the neurogenic cell population that exists in the dentate subgranular zone (SGZ) of the hippocampus (Andres-Mach, Rola, & Fike, 2008). The pattern of hippocampus-dependent memory dysfunction is consistent with the change in neurogenesis after acute irradiation. It is suggested that a relatively low dose of acute radiation sickness (ARS) in adult ICR mice is sufficiently detrimental to interrupt the functioning of the hippocampus, including learning and memory, possibly through the inhibition of neurogenesis (Kim, Lee, Kim, Kang, Bae, Shin, et al., 2008). The cognitive impairments are associated with reductions in proliferating Ki-67-positive cells and Doublecortin-positive immature neurons in the SGZ of the dentate gyrus. The significant loss of proliferating SGZ cells and their progeny suggests a contributory role of reduced neurogenesis in the pathogenesis of radiation-induced cognitive impairments (Raber, Rola, LeFevour, Morhardt, Curley, Mizumatsu, et al., 2004). Thus, the radiation response of neural precursor cells from SGZ of the hippocampal dentate gyrus cell and altered neurogenesis may play a contributory if not causative role in radiation-induced cognitive impairment (Mizumatsu, Monje, Morhardt, Rola, Palmer, & Fike, 2003). Progressive learning and memory deficiencies following irradiation may be caused by the accumulating hippocampal dysfunction that results from a long-term absence of normal stem/progenitor activity (Monje & Palmer, 2003).

Analyses of transcriptome profiles of mouse brain tissue after whole-body irradiation showed that low-dose exposures (10 cGy) induced genes not affected by high-dose radiation (2 Gy) and that low-dose genes were associated with unique pathways and functions. The molecular response of the mouse brain within a few hours after low-dose irradiation involves the down-regulation of neural pathways associated with cognitive dysfunctions that are also down-regulated in normal human aging and Alzheimer’s disease (Lowe, Bhattacharya, Marchetti, & Wyrobek, 2009).
Thus, there is new evidence for the radiation-induced molecular and cellular basis of CNS effects following exposure to low doses of ionizing radiation: disrupted neurogenesis in the adult hippocampus, changes in the gene expression profile, a neuroinflammatory response, neurosignaling alterations, apoptotic cell death, cell death and injury mediated by secondary damage, etc. together with the well-known role of the “glial-vascular union” in the pathogenesis of radiation brain injury.

2.2 Radioneuroembryological effects

The developing brain is extremely radiosensitive. Severe mental retardation, lowering of intelligence quotient (IQ), and worsening of school performance, or the occurrence of microcephalia and seizures, especially after exposure at 8–15 and 16–25 weeks after fertilization, were revealed in survivors of the atomic bombing of Hiroshima and Nagasaki (Otake & Shull, 1984, 1998; ICRP Publication 49, 1986; Shull, 1997; Shull & Otake, 1999; ICRP Publication 90, 2003). The latest reanalysis of the dosimetry data indicates that the dose threshold for the development of mental retardation after intrauterine irradiation at gestation ages of 8–15 weeks is 0.06–0.31 Gy. At a gestation age of 16–25 weeks, it is 0.28–0.87 Gy (Otake, Schull, & Lee, 1996). The question whether irradiation in utero is the risk factor for the increased lifetime prevalence of schizophrenia in survivors prenatally exposed to atomic bomb radiation is still open to discussion (Imamura, Nakane, Ohta, & Kondo, 1999).

The current thinking on prenatal radiocerebral effects is that 1 Sv of fetal exposure at 8–15 weeks of gestation reduces IQ by 30 points. Correspondingly, it is assumed that each 100 mSv of prenatal irradiation lowers IQ no more than 3 points. The excess of severe mental retardation is 0.4 per 1 Sv at 8–15 weeks and, to a lesser extent, at 16–25 weeks of gestation (European Commission. Radiation protection 100, 1998; ICRP Publication 84, 2000).

Thus, the evidence-based radioneuroembriologic effects in humans are: 1) dose-related intelligence reduction including mental retardation, 2) microcephalia, and 3) seizures. This IQ deterioration is dependent on the period of cerebrogenesis when the exposure has occurred. However, other possible radioneuroembriological effects, such as schizophrenia and epilepsy, are still at issue.

The data concerning brain damage in utero following the Chernobyl accident is very contradictory, as shown in Table 1. Extrapolation of Japanese findings to those from Chernobyl is limited. The Chernobyl accident caused lower fetal doses but significantly much higher doses on the fetal thyroid because of the radioiodine released by the burning reactor. Whereas after the Chernobyl accident the population was continuously exposed to radionuclides, mainly of radiodine and $^{137}$Cs, the Japanese population was acutely irradiated by γ-rays and neutrons. There was no separate radioiodine exposure of the thyroid in Japan. Because of the different radiobiological situations, it is not easy to predict the radiobiological effect of the Chernobyl accident from the results of the Japanese studies (Nyagu, Loganovsky, Pott-Born, Repin, Nechayev, Antipchuk et al., 2004).

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In 1992–1995, the World Health Organization (WHO) conducted the Pilot Project on Brain Damage in Utero under the auspices of the International Program on the Health Effects of the Chernobyl Accident (IPHECA). Analysis of the results in Belorussia, Russian Federation, and Ukraine has shown the following: a) the prevalence
of mild mental retardation in prenatally irradiated children is higher when compared with the control group; b) an upward trend was detected in cases of behavioral disorders and in changes in the emotional problems in children exposed in utero; and c) the prevalence of borderline nervous and psychological disorders in the parents of prenatally irradiated children is higher than that of controls. The IPHECA study had several crucial limitations of which the most important was the impossibility of linking the results to individual doses. The definition of an exposed and unexposed child was based only on the contamination level of the soil of the district of residence, without reference to individual doses (WHO, 1996).

Nyagu and colleagues (1992–2004) have paid great attention to the problem of brain damage in utero following the Chernobyl accident. In their first reports, an overestimation of mental development delay rate (up to 77%) was done, and the exposure of the thyroid in utero to doses more than 0.3 Sv was concluded to be the risk factor for neuropsychiatric effects (Nyagu, Cheban, Salamatov, Limanskaja, Yashchenko, Zvonariova, et al., 1993; Nyagu, Cheban, Bugayev, Korol, & Treskunova, 1997). Further, using international psychometric methodology, we found an increase of mild mental retardation and borderline low range IQ, as well as emotional and behavioral disorders and a decrease in high IQ, in children irradiated in utero. One important biological mechanism in the genesis of mental disorders in prenatally exposed children could be the radiation-induced malfunction of the thyroid-pituitary system with the effect threshold of 0.3 Sv of thyroid exposure dose. The data obtained reveal mental disorders in prenatally irradiated children and obviously reflect developmental abnormalities of brain structure and function as a result of the interaction of prenatal and post-natal factors, where it is possible to assume radiation effects on the developing brain (Nyagu, Loganovsky, Loganovskaja, & Antipchuk, 1996; Nyagu, Loganovsky, Cheban, Podkorytov, Plachinda, Yuriev, et al., 1996; Nyagu, Loganovsky, & Loganovskaja, 1998). The following were observed in the prenatally exposed group: IQ performance/verbal discrepancies with verbal decrements; a higher frequency of low-voltage and epileptiform EEG-patterns and left hemisphere lateralized dysfunction; and an increase of α- and β-power and a decrease of α- and θ-power; an increased frequency of paroxysmal and organic mental disorders, somatoform autonomic dysfunction, disorders of psychological development, and behavioral and emotional disorders. Cerebral dysfunction was recognized to be etiologically heterogeneous (Nyagu, Loganovsky, Loganovskaja, Repin, & Nechaev, 2002).

Igumnov (1996) showed that mental disorders among children irradiated in utero resulted from predominantly sociodemographic and socio-cultural factors. An increased prevalence of specific developmental speech-language and emotional disorders as well as a lower mean full scale IQ and more cases of borderline IQ in prenatally exposed children in Belarus were attributed to social and psychological factors. They did not find any association between prenatal irradiation and IQ and deterioration in children’s mental health (Igumnov, 1999; Kolominsky, Igumnov, & Drozdovitch, 1999). This point of view has been supported in the Annex J. Exposures and effects of the Chernobyl accident of the UNSCEAR 2000 Report to the General Assembly (2000). It was concluded that probably a significant role in the genesis of borderline intellectual functioning and emotional disorders in children exposed in utero in Belarus was played by unfavorable social-psychological and sociocultural factors (Igumnov & Drozdovitch, 2004).

There are data on intelligence reduction from thyroid doses of above 0.5 Gy for children exposed in utero and at the age of 0–1.5 years (Bazyltchik, Drozd, Reiners, & Gavrili6, 2001). Average IQ for the subgroup of highly exposed children (thyroid doses in utero >1 Gy) was lower in comparison with average IQ for the whole exposed group (Igumnov & Drozdovitch, 2000). Prenatally irradiated children, especially those exposed at 8–15 weeks, had more functional and organic disorders of the CNS and exhibited borderline IQ and abnormal EEG linked to both radiation and psychosocial factors (Gayduk, Igumnov, & Shalkevich, 1994). Children irradiated in utero had the highest indices of mental morbidity and were more likely to display borderline intelligence and mental retardation that were linked to prenatal irradiation (Ermolina, Sukhotina, Sosyukalo, Kashnikova, & Tatarova, 1996).

Recent studies using standard batteries of neuropsychological tests failed to find systematic differences in children exposed in utero (Litcher, Bromet, Carlson, Squires, Goldgaber, Panina, et al., 2000; Bar Joseph, Reisfeld, Tirosil, Silman, & Rennert, 2004). Interestingly, in the Litcher and colleagues (2000) study, mothers of evacuee children were 4 times more likely to report that their children had memory problems compared to controls even though there were no differences in actual neuropsychological test performance or school grades. This underscores the important contribution of perceived threat to reports about health and mental health status. However, no dosimetric data were available, and there were no normative data in Ukraine for the measures used in the study (Bromet, Goldgaber, Carlson, Panina, Golovakha, Gluzman, et al., 2000; Litcher, Bromet, Carlson, Squires, Goldgaber, Panina, et al., 2000). Moreover, the IQ tests were applied selectively: Litcher and colleagues (2000) assessed children’s cognitive functions using spatial intelligence (Symbolic
Relations subtest of the Detroit Test), attention, and memory only and excluded verbal intelligence. Full scale IQ, verbal IQ, and performance IQs are not available.

It was assumed that western-based investigations indicated that no adverse neuropsychiatric effects occurred in persons exposed in utero, but local studies reported increased cognitive impairments in exposed compared with non-exposed children. At the same time, the experts of the UN Chernobyl Forum (WHO, 2006) stressed that the effects on the developing brain should be the focus of attention after the Chernobyl accident. Taormina and colleagues (2008) conducted an 8-year follow-up of the evacuees and classmate controls assessed in Kiev in 1997. This study re-examined the children’s performance and academic achievement at age 19 years. The authors came to the conclusion that Chernobyl did not influence the cognitive functioning of exposed infants (including those irradiated in utero) although more evacuee mothers still believed that their offspring had memory problems. According to the authors’ opinion, these lingering worries reflect a wider picture of persistent health concerns as a consequence of the accident (Taormina, Rozenblatt, Guey, Gluzman, Carlson, Havenaar, et al., 2008). However, this study has also no assessment of the doses in utero.

Since possible dose correlations were not investigated and contradictory results of the mental health assessment of the in utero exposed children and the etiology of the observed neuropsychiatric disorders were found, a thorough study in the framework of Project 3 “Health Effects on the Chernobyl Accident” of the Franco-German Initiative for Chernobyl on potential effects of prenatal irradiation on the brain as a result of the Chernobyl accident has been performed. A cohort of 154 children born between April 26th, 1986, and February 26th, 1987, to mothers who had been evacuated from Pripyat to Kiev and 143 classmates from Kiev were examined with the Wechsler Intelligence Scale for Children (WISC) and the Achenbach and Rutter A(2) tests. Mothers were tested for their verbal abilities (WAIS), depression, anxiety, and somatization (SDS, PTSD, GHQ 28). Reconstruction of the individual doses received by the children was carried out considering internal and external exposure. ICRP Publication-88 (2001) was applied for calculation of effective fetal, brain, and thyroid internal doses for children of both groups. There were 52 children from Pripyat (33.8%) who had been exposed in utero to equivalent thyroid doses >1 Sv; 20 of these children (13.2%) had been exposed in utero to fetal doses >100 mSv. The prenatally exposed children had no excess of severe mental retardation and microcephaly; however, they exhibited significantly more psychological developmental disorders, emotional and behavioral disorders, organic mental disorders, and paroxysmal disorders. Exposed children exhibited lower full-scale IQs due to lower verbal IQs and therefore an increased frequency of performance/verbal intelligence discrepancies. When IQ discrepancies of the prenatally irradiated children exceeded 25 points, there appeared to be a correlation with the fetal dose. The exposed and control mothers did not show differences in verbal abilities, but the exposed mothers had experienced many more stressful events and had more depression, PTSD, somatoform disorders, anxiety/insomnia, and social dysfunctions than the control mothers from Kiev (Nyagu, Loganovsky, Pott-Born, Repin, Nychayev, Antipchuk, et al., 2004).

Consistent with our studies, Chernobyl exposure during gestation had a significant effect on behavior in adolescent offspring in Finland. Adolescents who were exposed from the second trimester in pregnancy onwards had a 2.32-fold risk (95 % CI: 1.13 – 4.72) of having lifetime depression symptoms, an increased risk of fulfilling DSM-III-R criteria of a Major Depressive Disorder (OR = 2.48, 95 % CI: 1.06 – 5.7), and a 2.01-fold risk (95 % CI: 1.14 – 3.52) of having attention deficit hyperactivity disorder (ADHD) symptoms. No associations with anxiety conduct disorder or oppositional defiant disorder symptoms were found. The authors concluded that perturbations in fetal brain development may have resulted in increased prevalence of depressive and ADHD symptoms after prenatal stress exposure from second trimester onwards (Huijzink, Dick, Sihvola, Rose, & Kaprio, 2007). In a relevant study they examined the potential effect of prenatal stress associated with the Chernobyl disaster in an ongoing genetic epidemiological study in Finland. Cortisol levels in both sexes and testosterone levels among females were significantly elevated after prenatal exposure to maternal stress from the second trimester onwards, compared to reference groups of nonexposed adolescents. Exposure explains 3% of variance in cortisol levels and 18% of variance in testosterone levels. No significant differences were found for exposure from either first or third trimester onwards. The results suggest that prenatal exposure to maternal stress in the second trimester of pregnancy may have resulted in prenatal programming of physiological systems relating to cortisol and testosterone levels (Huijzink, Bartels, Rose, Pulkkinen, Eriksson, & Kaprio, 2008).

In accordance with the above mention data, a study was conducted on cognitive functions on subjects in Sweden prenatally exposed to radioactive contamination following the Chernobyl accident. In a comprehensive data set of 562,637 Swedes born during 1983–1988, the cohort in utero during the Chernobyl accident was found to have had worse school outcomes than adjacent birth cohorts, and this deterioration was largest for those exposed approximately 8–25 weeks post conception. Moreover, larger damage was found among students born in regions that received more fallout: students from the eight most affected municipalities were 3.6 percentage...
points less likely to qualify for high school as a result of the fallout. These findings suggest that fetal exposure to ionizing radiation damages cognitive ability at radiation levels previously considered safe (Almond, Edlund, & Palme, 2007).

A radioneuroembriological effect — intelligence disharmony due to verbal IQ deterioration — caused by the accident at Chernobyl has been revealed at 8 and later weeks of gestation with a fetal dose >20 mSv and thyroid doses in utero >300 mSv and at 16–25 weeks of gestation with a fetal dose >10 mSv and thyroid dose in utero >200 mSv. Spectral θ-power decrease (particularly, in the left fronto-temporal area), β-activity increase together with its lateralization towards the dominant hemisphere, and disorders of normal interhemispheric asymmetry of visual evoked potentials and the vertex-potential can be considered as the neurophysiological markers of prenatal exposure. The most critical periods of cerebrogenesis resulting from the release of radioactive iodine into the environment are the later terms of gestation (16–25 weeks) rather than the earlier 8–15 weeks (Loganovskaja & Nechayev 2004; Loganovskaja, 2004, 2005). The frequency of mental disorders and personality disorders due to brain injury or dysfunction; disorders of psychological development; paroxysmal states (headache syndromes, migraine, and epileptiform syndromes); somatoform autonomous dysfunction; and behavioral and emotional disorders of childhood increased among these children (Napreyenko & Loganovskaja, 2004; Loganovskaja, 2005).

We reported earlier that there was prominent impairment of the left, dominant, cerebral hemisphere functions, especially its cortico-limbic structures, in children irradiated in utero as a result of Chernobyl (Loganovskaja & Loganovsky, 1999). Finally, we came to the conclusion that development of the dominant (left) hemisphere was disrupted following prenatal exposure as a result of the Chernobyl accident. The exposed children were found to have more neuropsychiatric disorders, left-brain neurological signs, lower full-scale and verbal IQs, IQ discrepancies with verbal decrement, disorganized EEG patterns, an excess of lateralized-to-left front temporal region delta and beta power with depression of theta and alpha power, and interhemispheric inversion visual information processing. Their mothers’ mental health, stress, and prenatal irradiation contributed to these effects, along with several confounding factors. These findings could reasonably be considered to be the basis for the neurodevelopmental hypothesis of schizophrenia (Loganovsky, Loganovskaja, Nechayev, Antipchuk, & Bomko, 2008). Recently, important experimental radioneuroembryological research on nonhuman models of schizophrenia has also supported the hypothesis that prenatal exposure of brain tissue to ionizing (X-ray) radiation may be associated with an increased risk of schizophrenia later in life, making schizophrenia a neurodegenerative and, probably, a neurodevelopmental disease (Korr, Thorsten Rohde, Benders, Dafotakis, Grolms, & Schmitz, 2001; Gelowitz, Rakic, Goldman-Rakic, & Selémon, 2002; Schindler, Wang, Selémon, Goldman-Rakic, Rakic, & Csernansky, 2002; Schmitz, Born, Dolezel, Rutten, de Saint-Georges, Hof, & Korr, 2005; Selémon, Wang, Nebel, Csernansky, Goldman-Rakic, & Rakic, 2005).

Thus, recent reports reveal that sub-clinical damage to human fetuses can result in cognitive deficits and other neuropsychiatric disorders. These previously unrecognized, long-term effects are apparently produced by a relatively short amount of exposure to radioactive fallout at levels that were previously thought not to be deleterious (Nowakowski & Hayes, 2008).

Obviously, a life span study should be done for the cohort of persons prenatally irradiated as a result of the Chernobyl accident, as well as those exposed at the age of 0–1 years. These survivors are under increased risk of a variety of neuropsychiatric disorders, including schizophrenia. The onset of these disorders can occur at any time in a person’s life.

2.3 Long-term cerebral effects of low-doses radiotherapy in childhood

CNS radiotherapy in infancy and childhood may have serious long-term neuropsychiatric effects. As the treatment of childhood cancer has improved, long-term survival has become more common, and, consequently, the delayed cerebral effects are now recognized (Anderson, 2003). However, it was, and still it is, assumed that the lowest dose to the brain that could be associated with late deterministic effects of childhood irradiation is 18 Gy, associated with disorders of cognitive functions, histopathological changes, and neuroendocrine effects (UNSCEAR 1993).

At the same time, evidence of delayed radiation brain damage (lower examination scores on scholastic aptitude, IQ, and psychological tests, completed fewer school grades, increased risk for mental hospital admissions, slightly higher frequency of mental retardation, and EEG abnormalities) was revealed 20 years after childhood scalp irradiation in average doses to the brain of only 1.3 Gy in a cohort of nearly 20,000 Israeli children exposed to X-ray irradiation of the head for ringworm (tinea capitis) management (Yaar, Ron, Modan, Perets, & Modan, 2008).
Among these persons 40 years after radiotherapy (the mean estimated radiation dose to the brain was 1.5 Gy), excessive relative risks per 1 Gy were observed for benign meningiomas and malignant brain tumors (Sadetzki, Chetrit, Freedman, Stovall, Modan, & Novikov, 2005). The follow up study showed that exposure of the brain to X-ray radiation for the treatment of scalp ringworm infections early in childhood (before 5 years of age) is associated with an increased risk of schizophrenia later in life. Preliminary findings suggested that those exposed early had more than a two-fold, statistically significant increase in schizophrenia risk when compared with unexposed siblings. Increased schizophrenia risk also correlated with a higher X-ray dose exposure (Gross, 2004). An increased risk of schizophrenia and related disorders was clearly seen among survivors who had been treated with radiotherapy of brain tumors in childhood or adolescence, as illustrated in a nationwide, population-based, retrospective cohort study in Denmark (Ross, Johansen, Dalton, Møllemkjær, Thomassen, Mortensen, & Olsen, 2003).

Recently, the effect of low doses of ionizing radiation (>100 mGy) in infancy (radiotherapy of cutaneous haemangioma) on cognitive function in adulthood has been proven on the basis of a Swedish population based cohort study. This is very striking, as the head dose in childhood following X-ray CT was 120 mGy and was higher than the cognitive deficit threshold (100 mGy). Obviously, the risk-benefits of CT for mild brain injury among children should be reassessed (Hall, Adami, Trichopoulos, Pedersen, Lagiou, Ekbom, et al., 2004). In this study, a negative dose-response relationship was evident for verbal IQ but not for performance IQ, testifying to impairment of the dominating (left) hemisphere. These data closely correspond to the deteriorating level of verbal IQ associated with open air nuclear testing (Graeub, 1994).

Thus, radiation exposure in childhood is obviously associated with dose-related cognitive decline in adulthood and neuropsychiatric disorders, including schizophrenia, later in life. The possible dose thresholds of delayed radiation brain damage are as low as 0.1–1.3 Gy to the brain in childhood. However, the lowest fraction and total doses on the brain causing neurocognitive effects are assumed to be 2 Gy and 18 Gy, correspondingly. Evidently, further studies have to be done for reassessment of the risk-benefit of long-term consequences of cranial radiotherapy and CT of the head in childhood.

### 2.4 Postaccidental neuropsychiatric radiation-related effects in adulthood

#### 2.4.1 Background

It is accepted in medical radiology that morphological radiation injuries of the CNS could arise following local brain irradiation by doses greater than 10–50 Gy. Radiation brain necrosis was observed at local brain exposure of 70 Gy and more, where the development of radiogenic dementia was considered to be a possibility. The tolerated dose on the brain was assumed to be 55–65 Gy and the tolerated fractional dose to be 2 Gy (Gus’kova & Shakirova, 1989; Gutin, Leibel, & Shelene, 1991; Mettler & Upton, 1995). Primary CNS damage following total body irradiation were assumed to be at an exposure >100 Gy (the cerebral form of Acute Radiation Sickness [ARS]) and secondary radiation CNS damage at an exposure of 50–100 Gy (the toxemic form of ARS) (Gus’kova & Bisogolov, 1971). The threshold for radiation-induced neuroanatomic changes was assumed to be at the level of 2–4 Gy of whole body irradiation (Gus’kova & Shakirova, 1989, Gus’kova, 2007).

However, in experimental studies morphological changes of neurons were revealed for as low as 0.25–1 Gy of total irradiation (Alexandrovskaja, 1959; Shabadash, 1964), and a dose of 0.5 Gy has been recognized to be the threshold of radiation injury to the CNS with primary neuronal damages (Lebedinsky & Nakhilnitzkaja, 1960). Persistent changes in brain bioelectrical activity occur at thresholds of 0.3 to 1 Gy and increase with the dose absorbed (Trocherie, Court, Gourmelon, Mestries, Fatome, Pasquier, et al., 1984). These data suggest that alteration in CNS functioning is likely to occur after relatively low doses of radiation (Mickley, 1987). It was shown that exposure to ionizing radiation significantly modifies neurotransmission (Kimeldorf & Hunt, 1965) resulting in multiple effects on the brain and behavior that depend largely on the dose received (Hunt, 1987). Slowly progressive CNS radiation sickness has been identified following a single exposure to total irradiation of 1–6 Gy (Moscalev, 1991). In the UNSCEAR Report (1982), it was noted that after exposure to 1–6 Gy, slowly progressive degeneration of brain cortex develops (Vasilescu, Pascalescu, Papilian, Serban, & Rusu, 1973). Thus, views on radiocerebral effects in adults are at issue.

#### 2.4.2 Epidemiological data

In the Adult Health Study in Hiroshima, the atomic bomb radiation dose did not show any significant association with detection of vascular dementia or Alzheimer’s disease 25 to 30 years later. Risk factors for
dementia were age, higher systolic blood pressure, history of stroke, history of hypertension, history of head trauma, lower milk intake, and lower education (Yamada, Sasaki, Mimori, Kasagi, Sudoh, Ikeda, et al., 1999; Yamada, Kasagi, Sasaki, Masunari, Mimori, & Suzuki, 2003). However, taking into account that increased blood pressure was the main contributor to vascular dementia (Yamada, Sasaki, Mimori, Kasagi, Sudoh, Ikeda, et al., 1999), it is important to note that in the same Adult Health Study a statistically significant effect of ionizing radiation on the longitudinal trends of both systolic and diastolic blood pressure was recently found. This phenomenon is compatible with the degenerative effect of ionizing radiation on blood vessels (Sasaki, Wong, Yamada, & Kodama, 2002). These recent analyses strengthen earlier findings of a statistically significant increase in non-cancer disease death rates with atomic bomb radiation dose. In particular, increasing trends are observed for diseases of the circulatory system (Shimizu, Pierce, Preston, & Mabuchi, 1999). There is direct evidence of radiation effects for doses of more than 0.5 Sv on heart disease, stroke, digestive diseases, and respiratory diseases (Preston, Shimizu, Pierce, Suyama, & Mabuchi, 2003).

Epidemiological studies of atomic bomb survivors have suggested dose-related increases in mortality from diseases other than cancer. Cardiovascular disease is one such non-cancer disease for which increases in both mortality and incidence have been found to be associated with radiation dose (Kusunoki, Kyoizumi, Yamaoka, Kasagi, & Kodama, 1999). The recognition in atomic-bomb survivors of non-cancer effects at doses on the order of 0.5 Sv (half the dose level considered a threshold in earlier studies) should stimulate interest in deterministic effects (Shimizu, Pierce, Preston, & Mabuchi, 1999; Fry, 2001; Preston, Shimizu, Pierce, Suyama, & Mabuchi, 2003) and non-cancer morbidity and mortality following the Chernobyl accident. However, the systematic review did not provide clear evidence of a risk of circulatory diseases at doses of ionizing radiation in the range 0–4 Sv, as suggested by the atomic bomb survivors. Further evidence is needed to characterize the possible risk (McGale & Darby, 2005).

The rate of schizophrenia in A-bomb survivors in Nagasaki was very high — 6% [60 per 1,000] (Nakane & Ohta, 1986), while the estimates of lifetime occurrence of schizophrenia vary from 0.9–6.4, and an estimate of the mean prevalence is 1.4–4.6 per 1,000 (Jablensky, 2000). Since 1990, there has been a significant increase in incidences of schizophrenia in the Chernobyl exclusion zone personnel (clean-up workers) compared to the general population (5.4 per 10,000 in the Chernobyl exclusion zone versus 1.1 per 10,000 in Ukraine, 1990) (Loganovsky & Loganovskaja, 2000).

Prior to the Chernobyl accident, consistent with the “healthy worker effect”, the clean-up workers (liquidators) had significantly lower rates of anxiety and alcohol disorders. However, the liquidators had significantly higher post-Chernobyl rates of depression (18.0% vs 13.1% in the Ukrainian population) and suicide ideation (9.2% vs 4.1%) after the accident but not alcoholism or intermittent explosive disorder. In the year preceding the interviews, rates of depression (14.9% vs 7.1%), posttraumatic stress disorder, PTSD (4.1% vs 1.0%), and headaches (69.2% vs 12.4%) were elevated. Liquidators affected with depression and PTSD lost more work days than affected controls. Exposure level was associated with current somatic and PTSD symptom severity. Thus, long-term consequences of the Chernobyl accident on the mental health of liquidators was observed. Further study is needed to collect more objective measures of exposure and physical health, consider possible cognitive impairment and psychotic symptoms, and conduct more rigorous psychiatric evaluations (Loganovsky, Havenaar, Tintle, Guey, Kotov, & Bromet, 2008). In the past, Inhabitants of radioactively contaminated zones have had increased risk of mental health symptoms and poor subjective health ratings. Thus, the long-term consequences of Chernobyl were observed in an unbiased sample of the general population of Ukraine (Havenaar, Bromet, Tintle, & Gluzman, 2007).

Radiation risks on non-cancer effects has been revealed in the liquidators (Biryukov, Gorsky, Ivanov, S., Ivanov, V., Maksioutov, Meskikh, et al., 2001; Buzunov, Strapko, Pirogova, Krasnikova, Kartushin, Voychulene, & Domashevkaya, 2001). For some classes of non-cancer diseases among liquidators, statistically significant estimates of radiation risk were derived for the first time. For mental disorders, excess relative risk (ERR) per 1 Gy was found to be 0.4 at a 95% confidence interval (0.17; 0.64); neurologic and sensory disorders were found to be 0.35 (0.19; 0.52); and endocrine disorders to be 0.58 (0.3; 0.87) (Biryukov, Gorsky, Ivanov, S., Ivanov, Maksioutov, Meskikh, et al., 2001). The highest ERR per 1 Gy was found for cerebrovascular diseases to be 1.17 (0.45; 1.88) (Ivanov, Maksioutov, Chekin, Kruglova, Petrov, & Tsyb, 2000).

Among Russian liquidators, statistically significant radiation risks were obtained for mortality from malignant neoplasms and cardiovascular diseases, while the risk of death from all non-cancer causes is close to zero and not statistically significant (Ivanov, Gorski, Maksioutov, Tsyb, & Souchkevitch, 2001). Recently, the statistically significant dose risk of ischemic heart disease (ERR per 1 Gy ERR Gy — 0.41 (0.05; 0.78)), essential hypertension (0.36 (0.005; 0.71)), and cerebrovascular diseases (0.45 (0.11; 0.80)) was published. The
at-risk group with respect to cerebrovascular diseases are those who received external radiation doses greater than 150 mGy in less than 6 weeks (RR —1.18 (1.00; 1.40)). However, radiation risks were not adjusted for recognized risk factors such as excessive weight, hypercholesterolemia, smoking, alcohol consumption, and others (Ivanov, Maksioutov, Chekin, Petrov, Biryukov, Kruglova, et al., 2006).

According to the data of the State Register of Ukraine and Clinical and Epidemiological Registry (Scientific Centre for Radiation Medicine, Kiev) there is an increased level of cerebrovascular disorders in liquidators and evacuees. Exposure to small doses of ionizing radiation is a significant risk factor of accelerating aging. Thyroid exposure by 300 mGy and more is a significant risk factor for vascular and cerebrovascular disorders. Thyroid exposure by 2 Gy and more is a significant risk factor for mental disorders, vascular and cerebrovascular diseases, and peripheral nervous system disorders. Exposure to doses of 250 mGy and more is a significant risk factor for neuropsychiatric disorders and vascular disorders. There is a dose–effect relationship for cerebrovascular disorders in liquidators. Non-radiation risk factors for neuropsychiatric pathology (cerebrovascular) include: industrial hazards, stress, smoking, heredity, and life style (Buzunov, Strapolko, Pirogova, Krasnikova, Kartushin, Voychulene, & Domashevskaya, 2001; Buzunov, Pirogova, Repin, Strapolko, Krasnikova, Prikashchikova, et al., 2001; National Report of Ukraine, 2006; Krasnikova & Buzunov, 2007). Therefore, it is clear that radiation from the Chernobyl accident has long-term neuropsychiatric effects. It is very evident that follow-up neuropsychiatric epidemiological studies with dosimetric support are necessary.

### 2.4.3 Neuropsychiatric consequences of Acute Radiation Sickness as a result of the Chernobyl accident

Immediately after the Chernobyl accident, autonomic [vegetative] vascular dystonia (VVD) and neurotic disorders were observed: at 0.8–2.1 Gy - mild ARS [or ARS of the 1st severity degree]; at 2–4 Gy - moderate ARS [or ARS of the 2nd severity degree] causing VVD; at 4.2–6.3 Gy - severe ARS [or ARS of the 3rd severity degree] causing acute radiation and radiation-toxic encephalopathy, acute psychosis with visual and acoustical hallucinations, and brain edema; at 6–16 Gy - very severe to lethal ARS [or ARS of the 4th severity degree] causing acute radiation and radiation-toxic encephalopathy, subarachnoidal-parenchimatosus hemorrhage, acute brain edema, and swelling (Torubarov, Blagoveshchestva, Chasal, & Nikolaev, 1989).

No clear signs of organic brain damage were registered during the first 3 years after irradiation in ARS-survivors; however, mental working capacity deterioration and asthenisation were in proportion to the severity of ARS. Further, progressive structural-functional brain damage — postradiation encephalopathy or postradiation organic brain syndrome — was revealed, and its diagnostic criteria were elaborated in the remote period of ARS according to neuropsychiatric follow-up studies (Nyagu, Loganovsky, Chuprovskaya, Vaschenko, Kostyuchenko, Zazimko, et al., 1997; Nyagu, Loganovsky, Yuryev, & Zdorenko, 1999; Nyagu, Loganovsky, & Yuryev, 2002; Nyagu, Loganovsky, Chuprovskaya, Kostyuchenko, Vaschenko, Yuryev, et al., 2003). The psychoorganic nature of mental disorders in the remote period of ARS was also supported by other studies; however, no dose–effects relationships were found (Revenok, 1998).

Vegeto-vascular and vegeto-visceral stages of neuropsychiatric pathology (3–5 years after irradiation) have changed with cerebral organic, cerebrovascular, and somatogenous neuropsychiatric disorders (5–10 and more years after irradiation). In 62% of patients who had confirmed ARS, there was postradiation organic brain syndrome. The apathetic type of organic personality disorder (microfocal neurological signs, personality changes, negative psychopathological symptoms, depression, and cognitive deficit) is characteristic of the neuropsychiatric consequences of ARS. This disorder has a progressive clinical course, its rate in proportion to the severity of ARS and, consequently, the radiation dose (Loganovsky, 2002; Nyagu, Loganovsky, & Yuryev, 2002; Loganovsky, Antipchuk, Bomko, Chuprovskaya, Kovalenko, Napreyenko, et al., 2007). Postradiation organic brain damage in the remote period of ARS has been verified by clinical neuropsychiatric, neurophysiologic, neuropsychological, and neuroimaging methods (Loganovsky, Kovalenko, Yuryev, Bomko, Antipchuk, Denisyuk, et al., 2003).

Three to five years after irradiation, irritated electroencephalographic (EEG) changes with paroxysmal activity shifted to the left frontotemporal region (cortical-limbic overactivation), transformed by irradiation toward a low-voltage EEG pattern with excess of fast (β) and slow (δ) activity together with depression of α- and θ-activity (organic brain damage with inhibition of the cortical-limbic system), were found to exist (Loganovsky & Yuryev, 2001). Among verified ARS-patients with qEEG, the neurophysiological markers of ionizing radiation (1–5 Gy) have been revealed: left fronto-temporal dominant frequency reduction; absolute δ-power lateralization to the left (dominant) hemisphere; relative δ-power increase in the fronto-temporal areas; absolute θ-power decrease in the left temporal region; and absolute and relative α-power diffusive decrease. This may
reflect cortico-limbic dysfunction lateralized to the left, dominant hemisphere, with fronto-temporal cortical and hippocampal damage (Loganovsky & Yuryev, 2004).

qEEG and evoked potentials data in the remote period of ARS testify to injury of the cortico-limbic system, mainly in the dominant (left) hemisphere, and central afferentation dysfunction of all sensoric modalities when sensoric information is processed by non-specific afferent systems while specific systems are inhibited (Loganovsky, 2000, 2002). A dose–effect relationship on mental working capacity deterioration was revealed for ARS patients (>1 Gy) (Zdorenko & Loganovsky, 2002).

Neuropsychological studies support the pathology of the frontal and temporal cortex of the dominant hemisphere and middle structures with their cortical–subcortical connections in the remote period of ARS. The inhibition of the left (dominant) hemisphere, together with compensative overactivation of the right hemisphere, was revealed. Neuropsychological dose–effects relationships were found for associative brain areas responding to movement control and regulation, mnestic (verbal), and sophisticated intellectual activity (Antipchuk, 2003, 2004, 2005).

Neuroimaging studies in the remote period of ARS have verified the cerebral organic nature of mental disorders and revealed the cortical atrophy of cerebral hemispheres, ventricular enlargement, and lacunar abnormalities. By morfometric analysis of MRI scans, neuroimaging markers of ionizing radiation (1–5 Gy) were obtained: decreasing of the contrast index of the left internal capsule and the contrast index of white matter of the left parietal and temporal lobes. Cortical atrophy of cerebral hemispheres and damage of neuronal pathways in the dominant hemisphere are the characteristic morphometric neuroimaging features of organic brain damage in the remote period of exposure to ionizing radiation as a result of the Chernobyl accident (Bomko, 2004, 2005).

Ultrasound dopplerographic studies of cerebral hemodynamics in the remote period of ARS have revealed the decrease of vessels’ involution, hemodynamic reactivity, and blood circulation in extracranial cerebral blood vessels. Characteristic changes in cerebral vessels are as follows: vasoospasm, tortuosity, stenosis, and asymmetry in internal carotid artery with the decrement of systolic circulation in the left internal carotid artery. The latter was recognized as the marker of radiation injury to cerebral vessels, and this artery was identified as the target for ionizing radiation (Denisyuk, 2006).

The characteristic and/or dose-related neuropsychiatric, neurophysiological, neuropsychological, and neuroimaging effects after ARS are lateralized in the dominant (left) hemisphere. This may testify to the radiovulnerability of this part of the brain to exposure of ionizing radiation (Loganovsky, Antipchuk, Bomko, Denisyuk, Loganovskaja, Chuprovskaja, et al., 2006). Postradiation brain damage is predominantly localized in the frontal areas of the left hemisphere and involves both white and gray matter of the brain. The functional and structural biomarkers of ionizing radiation have been established: cortical abnormalities (atrophic changes of frontal and temporal lobes) and damage to subcortical structures and neuronal pathways of the dominant hemisphere together with the cortical-limbic system, mainly in the dominant (left) hemisphere (Loganovsky & Bomko, 2004, 2007). Thus, the organic brain damage following ARS is ethyologically heterogenous as a result of both radiation and non-radiation risk factors. However, at exposure to 1 Sv and more, evidence of the crucial role of radiation has been revealed (Loganovsky, 2008).

2.4.4 Potential radiation-related neuropsychiatric effects following exposure to less than one Sv as a result of the Chernobyl accident

After the Chernobyl accident, peer reviewed publications relating neuropsychiatric consequences in exposed populations were dramatically increased; however, their main methodological limitation was an absence or lack of dosimetical assessment. At the same time, it is necessary to pay attention to the most important original studies published in different countries that empirically discovered the peculiarities of effects on the brain from exposure to low-dose radiation.

EEG-patterns and topographical distribution of spontaneous and evoked brain bioelectrical activity in overexposed liquidators, especially long-term workers in the Chernobyl zone, were significantly different in control and comparison groups (Niagu, Noshchenko, & Loganovskii, 1992; Noshchenko & Loganovskii, 1994). There are many consistent reports about characteristic neurophysiological (Danilov & Pozdeev, 1994; Zhavoronkova, Khlozodova, Zubovskii, Smirnov, Koptelov, & Ryzhov, 1995; Zhavoronkova, Khlozodova, Zubovskiy, Gogitidze, & Koptelov, 1995; Novikov, Tsagan, Borisova, & Rybina, 1997; Vyatleva, Kartagina, Puchinskaya, & Yurkin, 1997; Zhavoronkova, Khlozodova, Belostocky, & Kouljikov, 2008), neuropsychological
The progressive character of neuropsychiatric disorders and somatic pathology is observed in liquidators of 1986-1987, especially in those who worked for 3-5 years at the Chernobyl exclusion zone. The rate of neuropsychiatric disorders among personnel working since 1986-1987 and irradiated in doses above 250 mSv was 80.5% while for the same contingency, but irradiated in doses below 250 mSv the rate of these disorders was 21.4% only. Personnel in the Chernobyl exclusion zone who have been working since 1986 have the highest risk of neuropsychiatric disorders, where organic, including symptomatic, mental disorders dominate (Loganovsky, 1999).

While conventional EEG failed to reveal the dose-effect relationship, quantitative EEG allowed the discovery of radiation related peculiarities from a 0.3 Sv threshold as the increase of spectral power of δ- and β- activity shifted to the left fronto-temporal area together with a decrease in θ- and α-activity. Dose-related neuropsychiatric (mainly, negative psychopathology) and neurophysiological (Nyagu, Loganovsky, Yuryev, & Zdorenko, 1999; Loganovsky, 2000, 2002), neuropsychological or cognitive (Antipchuk, 2004, 2005), neuroimaging (Bomko, 2004, 2005), and cerebral hemodynamic (Denisyuk, 2006) abnormalities following exposure to >0.3 Sv were found. Those irradiated by moderate to high doses (more than 0.3 Sv) had significantly more left frontotemporal limbic dysfunction and schizophreniform syndrome (Loganovsky, 2000, 2002; Loganovsky & Loganovskaja, 2000).

Cytotoxic effects and humoral mechanisms (neuropeptides, brain antibodies, neurotropic lymphokines, and immune hormones) form a new view of the pathogenesis of neuropsychiatric effects following radiation exposure (Bazyka, Golyarnik, & Belyayeva, 2007). In clean-up workers exposed to 0.3-1 Sv, with organic brain damage considered to be a cerebrovascular pathology, the activation of HLA-DR+ lymphocytes under protein S-100 stimulation is revealed in comparison with those irradiated in doses lower 0.3 Sv. This probably testifies to an alteration of the glial structures in the CNS and a blood-brain barrier increasing in proportion to radiation dose (Khomenko, 2008).

A hypothesis about the development of Chronic Fatigue Syndrome (CFS) under the impact of low and very low doses combined with psychological stress has been suggested. CFS can be considered to be an environmentally induced predisposition and vestige of forthcoming neurodegeneration, cognitive impairment, and neuropsychiatric disorders (Loganovsky 2000, 2003; Volovik, Loganovsky, & Bazyka, 2005; Volovik, Loganovsky, Bazyka, Bebeshko, Cohen, Chao, et al., 2006). Moreover, CFS and metabolic syndrome X are considered to be both radiation-associated syndromes and stages of other neuropsychiatric and physical pathology developments, and CFS can be transformed into metabolic syndrome X. Radiation-induced damage of mitochondrial DNA in post-mitotic tissues with low proliferation activity may be a basis for the effects of low doses in an increase of non-cancer morbidity and mortality in the Chernobyl accident survivors (Kovalenko & Loganovsky, 2001). Currently, post-radiation syndrome is proposed to be CFS or a chronic fatigue syndrome-like illness, initiated by exposure to ionizing radiation. The symptoms and signs of post-radiation syndrome and its chronicity are similar or identical to those of CFS and can be explained as being a consequence of nitric oxide/peroxynitrite cycle etiology (Pall, 2008).

Accelerated aging and neurodegeneration are among potential low-dose radiation-induced phenomena (Bazyka, Volovik, Manton, Loganovsky, & Kovalenko, 2004; Bebeshko, Bazyka, Loganovsky, Volovik, Kovalenko, Korkushko, & Manton, 2006). Premature aging of clean-up workers was supported on the basis of comprehensive examinations. Data from an experimental study of primates irradiated with a dose of 1 Gy...
revealed formation of brain atrophy in the remote period after low dose radiation exposure (Kholodova, Zhavoronkova, Ryzhov, & Kuznetsova, 2007).

Another effect that could also be attributed to exposure to ionizing radiation is schizophrenia spectrum disorders (Loganovsky & Loganovskaja, 2000; Loganovsky, Volovik, Manton, Bazyka, & Flor-Henry, 2005). There are three hypotheses concerning ionizing radiation as a risk factor for schizophrenia: 1) genetic (in off-spring of exposed); 2) prenatal exposure (neurodevelopmental hypothesis), and 3) diathesis-stressor hypothesis (Loganovsky et al., 2005), while irradiation in adulthood is considered to be a new model of schizophrenia (Iwata, Suzuki, Wakuda, Seki, Thanseem, Matsuzaki, et al., 2008).

Obviously, these findings should be confirmed by mutual international studies, and the biological basis of low dose neuropsychiatric effects must be revealed.

2.5 Occupational exposure and neurotoxicity of Uranium and transuranium elements: implementation at the Shelter Object of the Chernobyl NPP

In the 1960s, it was commonly accepted that the nervous system reacts to exposure to low doses of ionizing radiation with vegetative (autonomous) vascular dystonia, asthenia, and, in proportion to radiation dose, organic CNS damage. However, after further assessment, the conclusion was reached that the threshold of radiation injury to the nervous system is 2–4 Sv of total irradiation. All other effects at exposure to lower doses are considered to be “functional” only (Gus’kova & Shakhirova, 1989; Gus’kova, 2007). The author finds this conclusion to be incorrect: there are not only “functional” disorders without a cerebral basis, but there are also technological limitations to their detection. Our position had been argued in detail above.

The available data on neuropsychiatric effects of occupational exposure are quite limited and contradictory. The most comprehensive related study was conducted by Azizova (1999) in atomic industry workers exposed to chronic occupational ionizing radiation, mainly external $\gamma$-irradiation. Vegetative-vascular dystonia, predominantly hypothensive, asthenic syndrome, and demyelinizing encephalomyelosis syndrome were the main neurological clinical patterns. Their rate was in proportion to the radiation dose. Together with hematological abnormalities (thrombocytopenia and leukocytopenia), these were considered to be the neurological features of Chronic Radiation Sickness. Demyelinizing encephalomyelosis was observed only at doses of 2–4 Sv and more. Cerebrovascular pathology was the most common in the remote period after irradiation. Radiation risk for cerebral atherosclerosis has been revealed; however, no connection between the dose and stroke rate has been found. Moreover, there was also no radiation-induced mortality excess from cardiovascular diseases in the workers of the “Mayak” radiochemical plant (Bolotnikova, 1994). It should be pointed out again that this systematic review does not provide clear evidence of a risk of circulatory diseases at doses of ionizing radiation in the range 0–5 Sv, as suggested by atomic bomb survivors. Further evidence is needed to characterize the possible risk (McGale & Darby, 2005).

At the same time, the increasing role of Uranium and transuranium elements (mainly Plutonium and Americium) has been shown in connection to the Chernobyl accident and the Shelter Object transformation to an ecologically safe system (National Report of Ukraine, 2006). In accordance with recent data on the neurotoxicity of Uranium (Lestaevel, Houpert, Bussy, Dhieux, Gourmelon, & Paquet, 2005), the same toxicity for transuranium elements can be reasonably supposed. It was shown that oxidative stress plays a key role in the mechanism of Uranium neurotoxicity, as well as in the double toxicity, chemical and radiological, of Uranium (Lestaevel, Romero, Dhieux, Ben Soussan, Berradi, Dublineau, et al., 2009). Neurophysiological examinations of Shelter Object personnel have revealed disorders of cerebral bioelectrical activity to be the basis for neuropsychiatric pathology development. Exposure to low and very low doses of ionizing radiation, neurotoxicity of Uranium and transuranium elements, stress, as well as other non-radiation industrial hazards were assumed to be possible risk factors (Loganovsky, Nechayev, & Perchuk, 2008).

The study of the biological effects of Uranium and transuranium elements is crucial for radiobiology, radiation hygiene, and psychophysiology. It is necessary to conduct large-scale studies in this field. The Shelter Object transformation to an ecologically safe system gives the unique possibility to study the radiotoxic effects of Uranium and transuranium elements on the human body.
3 CONCLUSION

The importance of constantly improving our knowledge and understanding of radiocerebral effects at low dose exposure is brought about by the current challenges of modern society and scientific and technological progress. We cannot and should not stop the evolution of man’s scientific inquiries: these obviously involve the development of nuclear energy and nuclear technologies, medical radiological procedures, as well as space flights. Unfortunately, this evolution is also associated with social risks, such as nuclear war or local military conflicts using depleted Uranium, radiation accidents, occupational and other overexposure, and radiological terrorist attacks. We have to be prepared for these eventualities by being armed with evidence-based scientific data to protect people and to distinguish between a radiation cerebral effect and panic. That is why it is now extremely necessary to integrate international efforts for further comprehensive studies of the health effects and the biological basis of exposure to ionizing radiation of humans, in general, and on the CNS, in particular.

The current data of possible dose thresholds for radiocerebral effects are summarized in Table 2.

Table 2. Dose thresholds for radiocerebral effects

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<tr>
<th>ADULTHOOD</th>
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<tr>
<td><strong>50–100 Gy</strong></td>
<td>Radiation brain damage (orthodoxally)</td>
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<tr>
<td>&gt;2–4 Sv</td>
<td>Radiation neurological signs (Gus'kova et al.)</td>
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<tr>
<td>&gt;1 Sv</td>
<td>Neurophysiological, neuroimaging markers and postradiation cognitive deficit (postradiation encephalopathy) RCRM data</td>
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<tr>
<td>&gt;0.3 Sv</td>
<td>Neuropsychiatric, neurophysiological, neuroimmune, neuropsychological, and neuroimaging dose-related effects RCRM data</td>
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<tr>
<td>&gt;0.15–0.5 Sv</td>
<td>Epidemiological data on radiation risks for cerebrovascular pathology (Ivanov et al., 2006; RCRM data; Shimizu et al., 1999; Preston et al., 2003)</td>
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<th>CHILDHOOD</th>
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<tr>
<td>&gt;1.3–1.5 Gy</td>
<td>Delayed cerebral effects (Ron et al., 1982; Yaar et al., 1982) – head irradiation</td>
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<tr>
<td>&gt;1.3–1.5 Gy</td>
<td>Cerebral tumors (Sadetzki et al., 2005) – head irradiation</td>
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<tr>
<td>&gt;1.3–1.5 Gy</td>
<td>Schizophrenia (Gross, 2004) – head irradiation</td>
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<td>&gt;0.1 Gy</td>
<td>Cognitive deficit (Hall et al., 2004) – head irradiation</td>
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<th>IN UTERO</th>
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<tr>
<td>0.06–0.31 Gy</td>
<td>at 8–15 gestation weeks – mental retardation (Otake et al., 1996)</td>
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<tr>
<td>0.28–0.87 Gy</td>
<td>at 16–25 gestation week – mental retardation (Otake et al., 1996)</td>
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<tr>
<td>Fetal dose &gt;20 mSv and thyroid dose in utero &gt;300 mSv</td>
<td>at +8th gestational weeks – neurophysiological and cognitive dose-related effects RCRM data</td>
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<tr>
<td>Fetal dose &gt;10 mSv and thyroid dose in utero &gt;200 mSv</td>
<td>at 16–25 gestational weeks – neurophysiological and cognitive dose-related effects RCRM data</td>
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Thus, it is very necessary to arrange international studies on neuropsychiatric effects of low doses and their biological basis together with the development of molecular, neuroimmunological, neurophysiological, and cognitive biomarkers of ionizing radiation.
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