Paper

PREDICTABILITY OF ACUTE RADIATION INJURY SEVERITY

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Abstract—**Results of dose-response analyses for different clinical symptoms of acute radiation syndrome (ARS) are reported here. The analyses were performed on dosimetric and clinical data from a group of ARS patients (59 cases) exposed to gamma and neutron or gamma radiation alone due to nuclear accidents at Mayak Production Association (Mayak PA). Findings suggested the possibility of prediction of injury severity within the first hours or days after acute exposure based on clinical symptoms and signs such as the onset of vomiting, neutrophil count abnormalities in the peripheral blood within the first 2–3 hours after acute exposure, and lymphocyte count abnormalities in the peripheral blood within the first 24–48 h after acute exposure.**

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Key words: accidents, nuclear; dose assessment; exposure, radiation; health effects

INTRODUCTION

In the past decades there have been an increasing number of individuals exposed to various sources of ionizing radiation. The possibility of radiation overexposures of nuclear workers as well as of general populations cannot be entirely prevented even if all safety regulations are met. Also, nowadays there is a real threat of nuclear terrorism with its possible adverse consequences for the general population. Medical radiation injury triage is critical in emergency situations such as large-scale radiation accidents, to facilitate the diagnostic classification of exposed individuals for prophylactic treatment or evacuation. Medical triage is based on the prediction of acute exposure effects and their severity from estimation of exposure dose. The most accurate prediction of injury severity degree is aided by knowledge of exposure dose measured by physical methods (Vasilenko et al. 2001). However, physical dosimetry would likely be unavailable during a large-scale radiation accident, especially within the first hours and even days after exposure. In such situations biological dosimetry, i.e., dose assessment based on biological parameters, is of particular importance for the prediction of injury severity.

The objective of this study was to analyze the relationship between the physical dose of acute radiation exposure and the biological effects, e.g., clinical symptoms and signs, to determine which of the latter can be reliably used for the prediction of the severity of the resultant injury.

MATERIALS AND METHODS

Mayak Production Association (Mayak PA), the first Russian nuclear enterprise located in the Southern Urals, was commissioned in June 1948. It included facilities necessary for weapons-grade plutonium production, e.g., industrial reactors, a radiochemical plant, and a plutonium production plant (Kruglov 2002). Due to the early lack of experience in operating nuclear facilities and the short time allowed by the government to accomplish weapons-grade plutonium production, 19 radiation accidents occurred during the start-up and early operations of Mayak PA, in the period from 1948 to 1958. They resulted in acute gamma-neutron or gamma exposures of 59 involved individuals who developed acute radiation syndrome (ARS). Of the 19 radiation accidents, three (15 March 1953; 22 April 1957; 2 January 1958) were associated with spontaneous criticality events producing high gamma and neutron exposures of nuclear workers (McLaughlin et al. 2000).

Descriptions, characteristics of the radiation accidents, and individual doses of acute exposure were provided by the Mayak PA Radiation Safety Department

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(RSD). Experts from Mayak PA collected and analyzed archival documents ("Acts of investigation of radiation accident") to reconstruct as completely as possible all the details of each accident in order to verify and reconstruct individual doses of acute exposure. The individual accident exposures used in this study are whole body absorbed doses. The individual criticality accident exposures include gamma and neutron doses. These whole body absorbed doses are verified estimates of acute exposures calculated based on the individual film badge readings and area dosimeters recording gamma exposures in the different points of the working areas. These dose estimates may undergo future modifications, particularly as regards the neutron component, as a result of the ongoing program of retrospective dose reconstruction at Mayak PA (Vasilenko et al. 2001).

It should be noted that from the very first days of Mayak PA operations, a system of medical monitoring was introduced and maintained for nuclear workers. It consisted of a compulsory pre-employment medical examination of all newly hired workers at Mayak PA, scheduled medical examinations once every 3 mo during 1948–1954; once every 6 mo during 1955–1960; and once every 12 mo from 1960 up to the present. In addition, workers routinely (once every 3–5 y) underwent expanded medical examinations in a specialized hospital (Clinic of Southern Urals Biophysics Institute, SUBI; former Branch No.1 of Biophysics Institute). After retirement, former Mayak workers have been followed-up by the same specialized medical hospital. This system of medical follow-up for Mayak nuclear workers has allowed the establishment of a unique archive of the primary medical data. It should be emphasized that individual dosimetry of external gamma radiation and monitoring of internal exposure due to incorporated ^{239}Pu were carried out on all of the

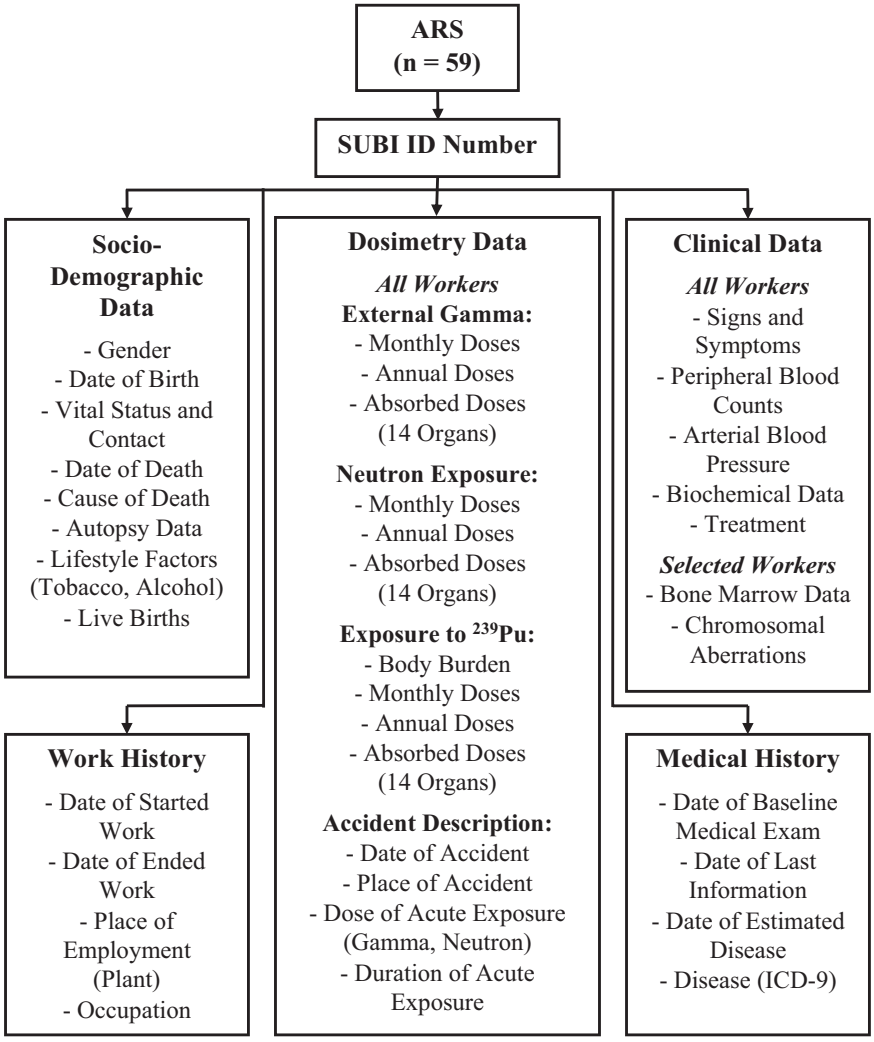

Fig. 1. Structure of the ARS clinical-dosimetry database for the Mayak worker cohort.

radiation workers since the start-up of Mayak PA. These data have been described in detail in the literature (Khokhryakov et al. 2000a and b, 2002; Romanov et al. 2002; Vasilenko et al. 2001).

The primary medical and dosimetric data were utilized to establish the ARS clinical-dosimetry database (Claycamp et al. 2000; Okladnikova et al. 2001). Fig. 1 illustrates the current structure of the database, which includes the identification (ID) number, passport and demographic information, work history, dosimetry data on external gamma and neutron radiation, internal exposure to ^{239}Pu including the shift; weekly, monthly, and annual exposure doses; absorbed doses to 14 organs; medical history; and clinical data for the whole period of follow-up (peripheral blood counts, bone marrow data, cytogenetic data, biochemical data, and morbidity). The ARS clinical pattern is also provided in detail from the first hours after exposure up to 90 d by 78 encoded clinical signs, which characterize the patient's health and status of the nervous, cardiovascular, respiratory, endocrine, bone-muscular, genitourinary, gastrointestinal, and visual systems, and skin. The ARS database includes extensive peripheral blood counts (erythrocytes, hemoglobin, reticulocytes, platelets, leucocytes, basophils, eosinophiles, metamyelocytes, band neutrophils, polymorphonuclear neutrophils, lymphocytes, monocytes, plasmocytes, etc., and erythrocyte sedimentation rate) from all patients for the whole period of follow-up.

In the Mayak worker cohort, 59 ARS patients, including 10 females, were diagnosed during 1950–1958. Table 1 shows a distribution of patients by the ARS severity degree based on the classification of Guskova and Baysogolov (Guskova and Baysogolov 1971; Guskova 2001b; Guskova et al. 2001). Their classification is roughly comparable to that of Thoma and Wald (1959) as follows: Severity Degree I of the Guskova and Baysogolov classification is similar to Injury Group II of the Thoma and Wald classification, Severity Degree II is similar to Injury Group III, Severity Degree III is similar to Injury Group IV, and Severity Degree IV is similar to Injury Group V.

It should be noted that retrospective clinical analysis of each case based on the Guskova and Baysogolov (1971) classification did not confirm the ARS diagnosis in a subset of patients in whom a mild ARS was diagnosed earlier. The involvement of these workers in radiation accidents was the main indication for their hospitalization in a specialized clinic. Intensive detailed examination resulted in the finding of unstable slight deviations in their health (e.g., unstable changes in the morphological composition of peripheral blood; slight vegetative and vascular disorders; subjective symptoms, etc.). These patients (14 individuals) were considered as a separate group "involved in a radiation accident" based on the data analysis. The subset corresponds to Injury Group I of Thoma and Wald (1959), where the stress of involvement in an accident may produce non-specific stress effects that cannot be distinguished from minimal radiation effects with any certainty.

Absorbed doses from accidental exposures of the workers ranged from 0.2 to 131.3 Gy. The ARS severity showed a direct relation to the magnitude of the absorbed dose of acute exposure (Table 2).

The work described in this paper has been monitored by Human Subjects Committees approved by the U.S. Health and Human Services Administration (Federalwise Assurance FWA00006759 dated April 12, 2004) at the Southern Urals Biophysics Institute and the University of Pittsburgh.

Statistical methods

Standard techniques such as the Kruskal-Wallis test, the Dunn test, and regression analysis (Zar 1999; Glantz 1999) were applied to the statistical processing and data analysis. In testing of the dose-response curves, the probit method was applied. The critical level of significance in testing of statistical hypotheses in this study was 0.05. The data are given as mean ± standard error.

RESULTS

The ARS typically progresses through several phases including a prodromal phase (i.e., primary response), a

Table 1. Distribution of Mayak PA workers with ARS (1948–1958) in accordance with ARS injury severity classification of Guskova-Baysogolov.

Guskova and Baysogolov (1971); Guskova (2001b); Guskova et al. (2001)		Mayak PA ARS cases (1948–1958)		
Severity degree	Estimated dose, rad[a]	Males (fatalities)	Females (fatalities)	Total (fatalities)
IV: most severe	≥600	6 (6)	1 (1)	7 (7)
III: severe	400–599	2	2	4
II: moderate	200–399	5	1	6
I: mild	100–199	25	3	28
0: involved in a radiation accident	<100	11	3	14
Total		49 (6)	10 (1)	59 (7)

[a] Historical units retained.

Table 2. Mean (median) absorbed external doses (Gy) in a radiation accident.

Severity degree	Males	Females	Both
IV	57.9 ± 22.9 (34.3)	46.0	56.2 ± 19.4 (46.0)
III	6.8 ± 2.8 (6.8)	12.1 ± 0.1 (12.0)	9.4 ± 1.9 (10.8)
II	4.3 ± 1.5 (3.0)	5.8	4.6 ± 1.2 (3.5)
I	1.4 ± 0.1 (1.5)	3.3 ± 1.4 (3.0)	1.6 ± 0.2 (1.5)
0	0.5 ± 0.1 (0.5)	1.3 ± 0.2 (1.5)	0.7 ± 0.1 (0.5)

latent phase (i.e., a transient clinical improvement), a critical phase (i.e., the height of clinical manifestations), and a recovery phase in survivors. It is known that the appearance and duration of each ARS phase depends on the exposure dose (Guskova and Baysogolov 1971; Guskova et al. 2001; Guskova 2001a and b; Selidovkin et al. 2001). Clinical patterns, frequency of symptoms and signs and their dose-dependence in prodromal and latent phases of ARS were analyzed in order to achieve the study objective.

Among the main clinical symptoms and signs noted in the ARS prodromal phase in Mayak workers were anorexia, nausea, vomiting, headache, dizziness, weakness, abdominal pains, diarrhea, vascular hypotonia (less than 90/60 mm of mercury), tachycardia (heart rate was over 80 beats per minute), and elevated body temperature (over 37°C) (Table 3). The frequency of such objective signs as vomiting, diarrhea, elevated body temperature, tachycardia, and vascular hypotonia or their combinations in the study group increased with exposure dose and relevant severity degree (Table 3). At the same time, the difference in the frequency of subjective signs at different ARS severity degrees was not significant.

Analysis of the onset of vomiting in patients with I–IV degrees of ARS severity using the Kruskal-Wallis test revealed statistically significant time differences. The Dunn test for multiple comparisons indicated that the time of onset of vomiting for group IV of ARS severity significantly differed from the time for groups I and II of ARS severity. However, due to insufficient statistical power it was impossible to reach significance for the rest of the groups.

The regression analysis revealed a significant linear interrelationship between the logarithm of time of vomiting onset and logarithm of absorbed acute dose (Fig. 2, based on the available data from 29 individuals). The median effective dose for vomiting based on the probit method was approximately 1.3 Gy with a 95% confidence interval of 0.5–3.9 Gy.

The hematopoietic system is known to be the most radiosensitive system (Thoma and Wald 1959; Guskova and Baysogolov 1971; Wald 1998; Guskova et al. 2001; Guskova 2001a; Selidovkin et al. 2001; Goans et al. 2001). Patterns of the peripheral blood counts (number of neutrophils, lymphocytes, platelets, and erythrocytes, L^{-1}) were analyzed in Mayak PA workers with different degrees of severity of ARS starting with the initial pre-accidental level and extending through the first seven days after acute exposure. Figs. 3–7 show patterns of peripheral blood counts (average values) within the first week after acute exposure.

The curve of the neutrophil count within the first 2–3 h after exposure demonstrates an increase of these blood cells in comparison with the initial level for all ARS severities (Fig. 3). However, the highest neutrophil count (more than 12×10^9 L^{-1}) was found in the peripheral blood from patients with degrees III–IV of ARS. A bimodal curve of neutrophils in the same groups within the first days after exposure was also noted (Fig. 3). An analysis of the neutrophils within the first 2–3 h after exposure showed a relationship to the acute dose. A significant direct linear dependence of the neutrophil count on the logarithm of acute dose is plotted in Fig. 8 (based on the available data from 22 individuals).

A sharp increase in neutrophil count was transient and of short duration, and followed by the decrease in neutrophil count in the peripheral blood from all the ARS patients. The degree of neutrophil deficiency (since the seventh day) and onset of agranulocytosis (Table 4), i.e.,

Table 3. Key clinical symptoms and signs of the ARS prodromal phase.

		ARS severity				
Symptom	Description	IV	III	II	I	0
Vomiting	Onset (h)[a]	0.3 ± 0.1 (0.08–0.5)	1.4 ± 0.4 (0.5–2)	2.3 ± 1.6 (0.5–4)	3.9 ± 0.8 (0.5–8)	9
	Percent (%)	100.0	100.0	100.0	42.3	7.7
Weakness (%)		85.7	75.0	66.7	23.1	50.0
Headache (%)		100.0	50.0	83.3	65.4	78.6
High temperature (%)		100.0	100.0	33.3	3.8	21.4
Diarrhea (%)		85.7	0.0	0.0	0.0	0.0
Abdominal pains (%)		71.4	50.0	50.0	39.3	14.3
Tachycardia (%)		100.0	100.0	100.0	75.0	78.6
Vascular hypotonia (%)		100.0	100.0	100.0	85.7	64.3

[a] Here and further in the tables (minimum value–maximum value).

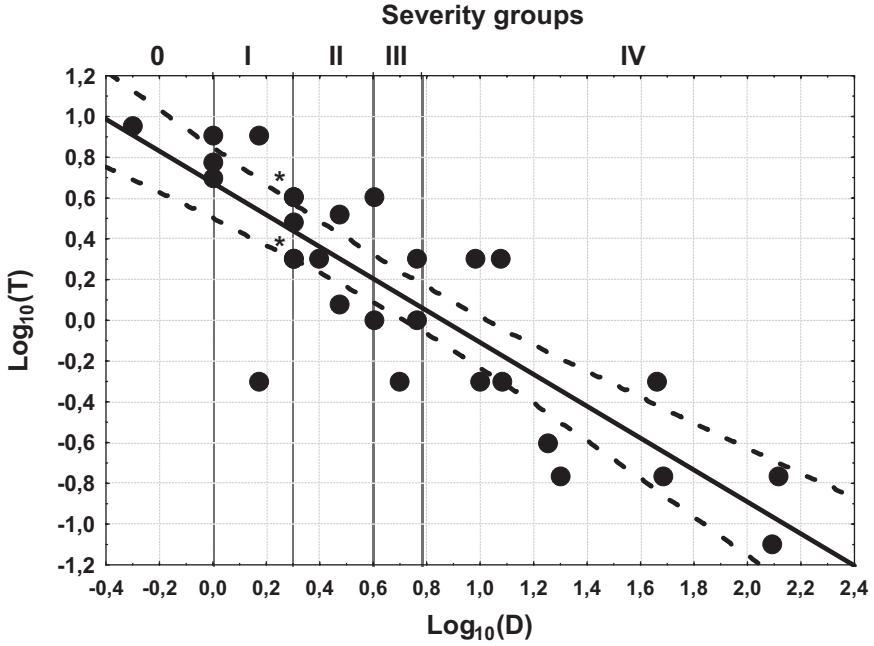

Fig. 2. Time-dependence of vomiting on absorbed acute dose (* = two patients): $\mathrm{Log}_{10}(T) = (0.67 \pm 0.08) - (0.78 \pm 0.09) \times \mathrm{Log}_{10}(D)$, $R^2 = 0.7$, where $\mathrm{Log}_{10}(T)$ is decimal logarithm of the vomiting onset; T is the vomiting onset (h); $\mathrm{Log}_{10}(D)$ is decimal logarithm of absorbed acute dose; and D is absorbed acute dose (Gy). (Here and in the following figures, dotted lines indicate the 95% confidence interval for the regression line.)

reduction below 0.5×10^9 L^{-1}, depended significantly on acute exposure dose.

On the second or third day, when prodromal symptoms receded (i.e., latent phase or a phase of illusory improvement), a decrease of lymphocyte count in the peripheral blood was observed due to the usually high radiosensitivity of these cells (Fig. 4). This was noted earlier by many other researchers (Thoma and Wald 1959; Baranov et al. 1990, 1995; Wald 1998; Goans et al. 1998; Friesecke et al. 1999).

The dependence of lymphocyte count on absorbed dose on the first to seventh days after acute exposure was studied. Analysis of the lymphocyte count in the peripheral blood on the second or third day after the accident showed a significant inverse linear dependence on the logarithm of acute dose (Fig. 9, based on the available data from 19 individuals). The higher the acute dose, the lower was the lymphocyte count observed in the peripheral blood (Figs. 4 and 9).

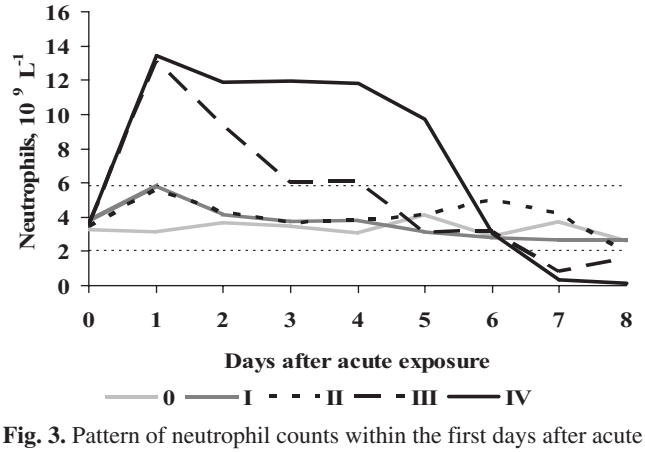

Fig. 3. Pattern of neutrophil counts within the first days after acute exposure. (0 are involved in a radiation accident, I is mild ARS, II is moderate ARS, III is severe ARS, IV is most severe ARS, and dotted lines are upper and lower norms (Vorobyev 2002).

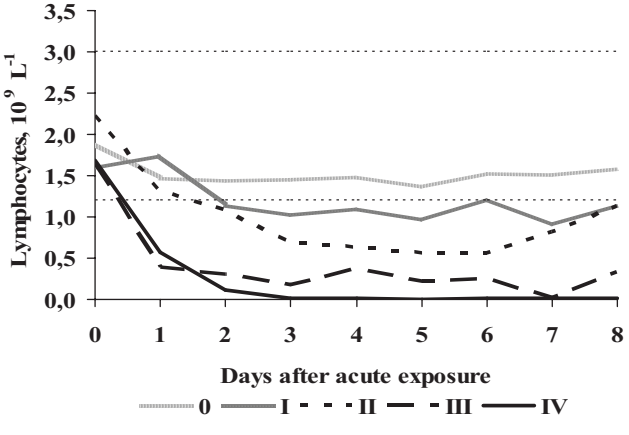

Fig. 4. Pattern of lymphocyte counts within the first days after acute exposure. (0 are involved in a radiation accident, I is mild ARS, II is moderate ARS, III is severe ARS, IV is most severe ARS, and dotted lines are upper and lower norms (Vorobyev 2002).

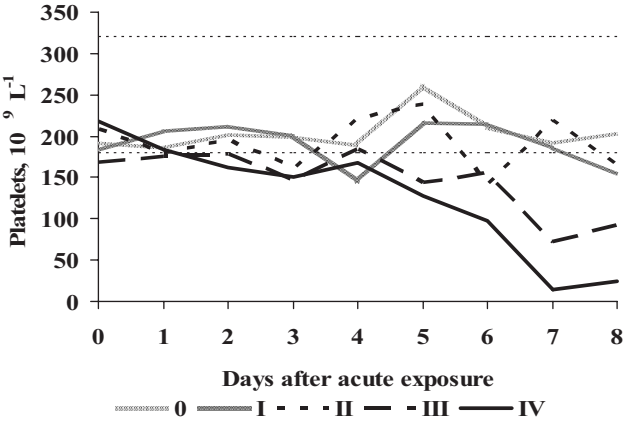

Fig. 5. Pattern of platelet counts within the first days after acute exposure. (0 are involved in a radiation accident, I is mild ARS, II is moderate ARS, III is severe ARS, IV is most severe ARS, and dotted lines are upper and lower norms (Vorobyev 2002).

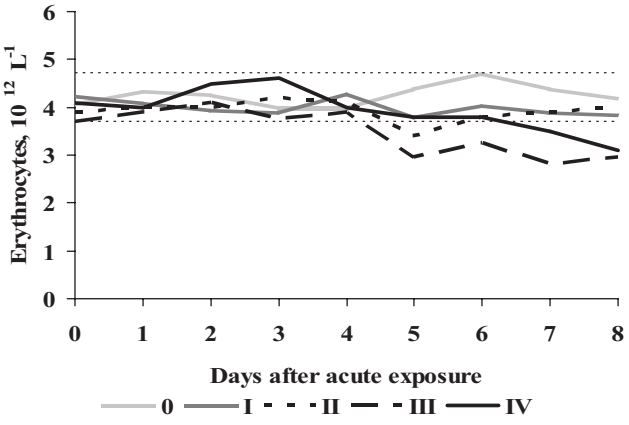

Fig. 7. Pattern of erythrocyte counts in females within the first days after acute exposure. (0 are involved in a radiation accident, I is mild ARS, II is moderate ARS, III is severe ARS, IV is most severe ARS, and dotted lines are upper and lower norms (Vorobyev 2002).

Platelet count in the peripheral blood ranged within the physiological norm during the first days after acute exposure (Fig. 5). Subsequent thrombopenia in the peripheral blood was observed in all ARS patients within the first to third weeks after acute exposure and platelet count in the peripheral blood was significantly dependant on acute exposure dose.

A reduction of erythrocyte count below 3.0×10^{12} L^{-1} was observed only in patients with degree IV of ARS (Figs. 7–8) at 7 d after acute exposure. In all other groups, levels of erythrocytes ranged within the physiological norm both in males and females. This could be explained by the high radioresistance of erythrocytes and their longer lifetime in the peripheral blood (Guskova and Baysogolov 1971).

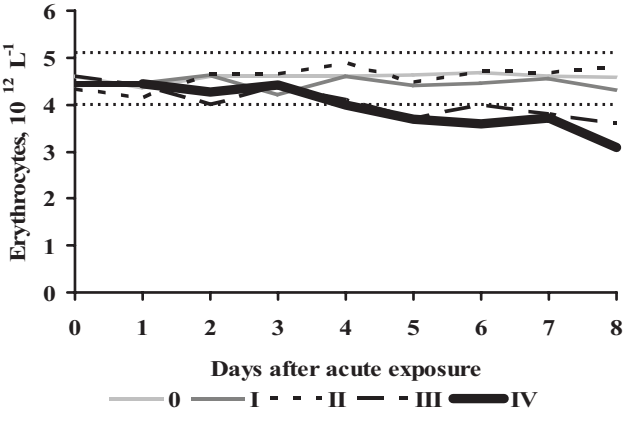

Fig. 6. Pattern of erythrocyte counts in males within the first days after acute exposure. (0 are involved in a radiation accident, I is mild ARS, II is moderate ARS, III is severe ARS, IV is most severe ARS, and dotted lines are upper and lower norms (Vorobyev 2002).

DISCUSSION

Prediction of the degree of injury severity is critical in emergency situations such as large-scale radiation accidents involving large populations, to facilitate decision-making for rendering the proper medical care within the first hours after acute exposure. The Chernobyl Nuclear Power Plant accident indicated that the first predictions of injury severity degrees were made based on doses estimated using methods of biological dosimetry (Guskova et al. 1988; Ilyin 1988; Pyatak et al. 1988). The methods of dose assessment based on clinical symptoms, signs and laboratory data have been developed for 50 years (Thoma and Wald 1959; Guskova and Baysogolov 1971; Baranov 1987; Wald 1998; Goans et al. 2001). At present, various additional biological methods of dose assessment and radiation exposure indication, such as cytological, cyto- and molecular-genetic, biochemical, and biophysical techniques, have been added (Melnov 2002). Their diversity indicates a lack of universal methodologies, and therefore our search for a practical approach was carried out.

The primary or prodromal response is known to be useful for acute exposure assessment and predicting the level of injury severity within the first hours after acute exposure (Thoma and Wald 1959; Guskova and Baysogolov 1971; Anno 1998; Goans et al. 1998; Kindler et al. 1998; Guskova 2001a; Selidovkin et al. 2001).

It is obvious that a combination of signs defines a clinical pattern of the prodromal syndrome. The results of this study indicate that the time to onset, and frequency and duration of vomiting are the most reliable and significant prognostic signs for acute dose assessment and subsequent prediction of injury severity within the first hours after acute exposure.

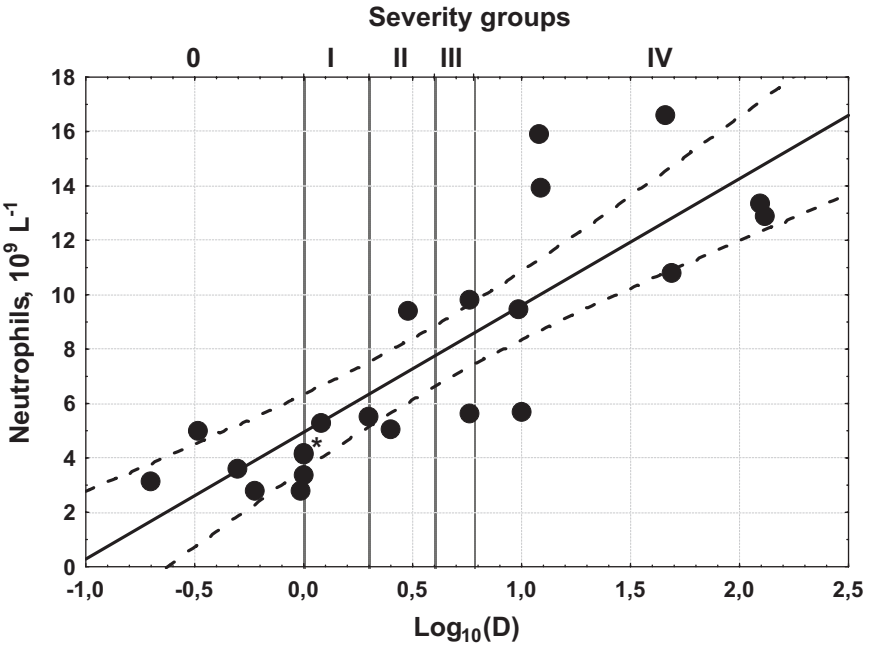

Fig. 8. Dependence of neutrophil counts on absorbed acute dose within the first hours after exposure (* = two patients): Neutrophils = (4.94 ± 0.66) + (4.66 ± 0.67) × $Log_{10}(D)$, R^2= 0.7, where Neutrophils is the neutrophil count ($\times 10^9$ L^{-1}); $Log_{10}(D)$ is the decimal logarithm of absorbed acute dose; and D is absorbed acute dose (Gy).

Diarrhea observed within the first 1 to 4 h after exposure in combination with the early and multiple vomiting episodes and severe weakness (i.e., when a patient is unable to walk) provides grounds to predict degree IV of ARS of the bone marrow and more severe ARS forms (intestinal, cardiovascular, and cerebral).

Significant linear dependence of the neutrophil count increase in the peripheral blood during the first two to three hours after acute exposure on the logarithm of absorbed acute dose was demonstrated in this study. Many investigators consider this transitory increase in neutrophil count to be one of the symptoms of the non-specific response (systemic inflammatory response syndrome) to any severe stress, including radiation injury (Shano et al. 1998). We propose the use of this sign in the prodromal phase in combination with other medical symptoms to assess the clinical significance of the exposure.

Table 4. The onset of agranulocytosis depending on the ARS severity.

ARS severity	Onset of agranulocytosis (day)	Patients with agranulocytosis (%)
IV	6.4 ± 0.2 (6–7)	100.0
III	14.0 ± 3.8 (7–20)	100.0
II	28.2 ± 1.6 (25–34)	100.0
I	32.7 ± 1.5 (30–35)	10.7
0	—	0.0

Lymphocytes are the most sensitive indicators of hematopoietic lesions. After acute exposure to 1–2 Gy, the lymphocyte count in the peripheral blood decreased to 50% of the normal level within 48 h (NRPB 1996). As has been demonstrated by many investigators, the dose-response curves of lymphocytes are a good "biodosimeter" and prognostic sign of ARS severity within the first 24 to 72 h (Thoma and Wald 1959; Baranov et al. 1990, 1995; Kindler et al. 1998; Wald 1998).

The dose-response curves of lymphocyte count plotted in the course of our study were consistent with the corresponding literature data and could serve as a practical biodosimeter for acute dose assessment as well as a diagnostic practical clinical predictor of injury severity within the first 24 to 48 h after acute exposure. Despite the limited number of cases with sufficient data (29, 22, and 19, respectively), the dose-response curves shown in Figs. 2, 8, and 9 could allow prediction of ARS severity based on the following measures: time of vomiting onset, neutrophil count in the peripheral blood during the first 2–3 h after acute exposure, and lymphocyte count in the peripheral blood during the first 24–48 h after acute exposure. These curves could also be used to estimate the magnitude of the acute exposure dose based on the quantitative extent of the indicated clinical signs. Later hematological testing (i.e., after the seventh day after acute exposure) in our study showed that the dose-response curves of neutrophil diminution and the close

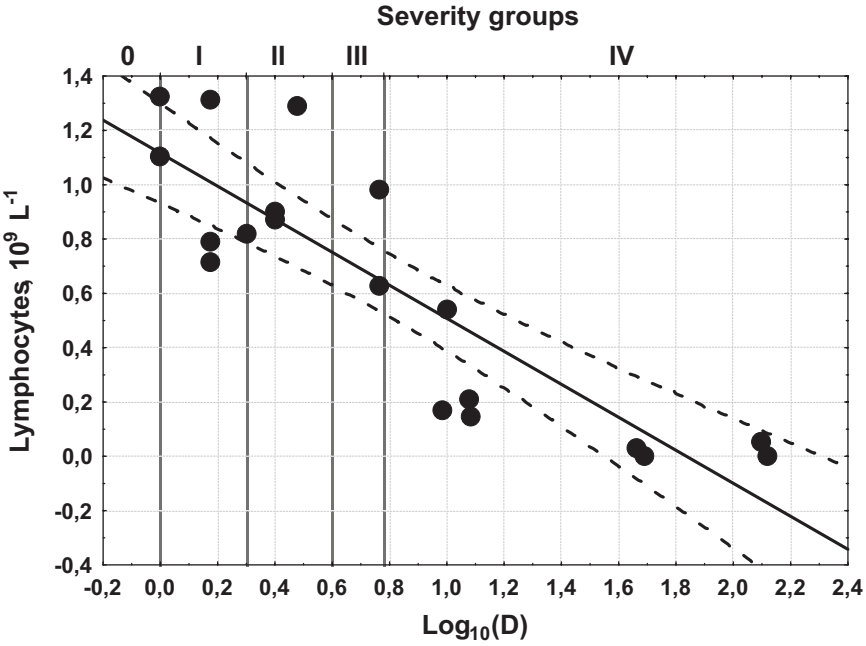

Fig. 9. Dependence of lymphocytes on absorbed acute dose on the third day after exposure: Lymphocytes = (1.12 ± 0.09) − (0.61 ± 0.08) × $Log_{10}(D)$, R^2= 0.7, where Lymphocytes is the lymphocyte count ($\times 10^9$ L^{-1}); $Log_{10}(D)$ is the decimal logarithm of absorbed acute dose; and D is absorbed acute dose (Gy).

relationship found between the onset of agranulocytosis and absorbed acute dose could also provide relatively accurate estimates of acute dose as well as a good measure of radiation injury severity.

Thus, results of this study showed that both a reasonable estimate of acute dose and a useful prediction of acute exposure consequences can be obtained as early as the first hours after acute exposure based on the clinical symptoms and signs. At the same time we recognize that resultant individual dose assessments have limitations and errors due to variations in individual radiosensitivity, non-uniformity of exposure distribution and other factors. If the purpose of the biomedical examinations is for patient care, their direct utilization as indicators of radiation injury severity for establishing an individual prognosis and treatment plan is probably most appropriate. We are now utilizing the information reported here to develop a simple, objective ARS patient injury severity classification system for non-radiation injury-trained front line responders in a radiation overexposure incident (Kuniak et al. 2008).

CONCLUSION

Results of the analysis of clinical data on 59 ARS patients from Mayak PA confirmed the possibility of acute absorbed dose estimation and prediction of injury severity within the first hours or days after acute exposure using the following clinical symptoms and signs: onset of vomiting; neutrophil count in the peripheral blood within the first 2–3 h after acute exposure; and lymphocyte count in the peripheral blood within the first 24–48 h after acute exposure.

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