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Radiation Toxins – Effects of Radiation Toxicity, Molecular Mechanisms of Action, Radiomimetic Properties and Possible Countermeasures for Radiation Injury

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1. Introduction

Radiation toxins induce high toxicity reactions after exposure

Acute Radiation Disease (ARD) or Acute Radiation Syndromes (ARS) are defined as the collective toxic clinical states observed from the acute pathological processes in various doses of irradiated mammals; to include: systemic inflammatory response syndrome (SIRS), toxic multiple organ injury (TMOI), toxic multiple organ dysfunction syndromes (TMODS), and finally, toxic multiple organ failure (TMOF). [2, 10, 18, 21] Moderate and high doses of radiation induces necrosis of radiosensitive cells with the subsequent formation of radiation toxins and their induced acute inflammatory processes. Radiation necrosis is the most substantial and most severe form of radiation induced injury, and when widespread, has grave therapeutic implications [1, 3, 53]. Low doses of radiation exposure induces apoptosis (controlled, programmed death of radiosensitive cells) without significant levels of specific radiation-induced toxin formation and with only low levels of inflammatory response [17, 50, 62].

Studying the trigger mechanism for radiation-induced lymphocyte death, N.I. Sorokina used the results of numerous experiments to show that ionizing radiation induces changes in the antigen phenotype of immature thymocytes in mice. This has the same type of effect as chemical differentiation inductors and thymotropin, which indirectly attests to the specific modifying effect of ionizing radiation [97, 98].

B.D. Zhivotovskiy described radiation-induced apoptosis and demonstrated a quantitative association between the pyknotic changes in the cell nuclei of thymocytes and production of postradiation chromatin decay products. The enzyme responsible for the decomposition of chromatin in irradiated cells is Ca/Mg-dependent endonuclease. Areas of endonuclease

attack are distributed randomly and are not associated with the level of repetition of nucleotide sequences of DNA or the transcriptional activity of chromatin. This supports the conclusion that the radiation death of lymphoid cells and the general biological phenomenon of programmed cell death are identical in nature [95, 96]. Apoptosis, interphase cell death of irradiated lymphocytes, is considered one example of the biological phenomenon known as "programmed cell death". Interphase cell death occurs as the result of "switching on" a specific genetic program, the triggering of which evokes induction of specific genes that switch on the "cell-death program". [1] Apoptosis may occur as the result of many signals, among which include: various types of lympholytic agents, different chemical agents, and physical factors which include ionizing radiation [15,50].

But relatively high doses of radiation could induce other forms of programmed cell death, apoptosis and/or necrosis. Necrosis especially, initiates inflammation and formation of specific Radiation Toxins (RTs) [62, 64, 65, 66, 89, 90, 91]. Specific Radiation Toxins are playing an important role as the trigger mechanism for inflammation, cell lysis, and damage to vital cellular structures such as mitochondria, DNA, ion channels and cell membranes [89, 90, 91, 92, 93, 94]. The mechanism and action of Radiation Toxins could be compared to actions of different microbial toxins, snake and scorpion venoms, enteric bacterial toxins, natural and plant-borne toxins [6, 86, 87, 88]. At high doses of radiation, specific Radiation Toxins play an important role in the development of pathological processes, especially injury to the central nervous system [89, 90, 91]. Radiation induces changes in concentration of many chemical mediators which possess significant influence on the Central Neural System - acetylcholine, cholinesterase, adrenergic amines, glutamate, γ -Aminobutyric acid, aspartic acid and interact with receptors and ions channels.[4, 30]. Many natural toxins like scorpion venom induce a prolongation of action potentials caused by selective inhibition of sodium current inactivation and specifically affect voltage-gated sodium channels in excitable tissues.[6, 29, 36, 44, 49, 60, 82, 83, 84, 85]. "Excitotoxicity" is an important pathological mechanism which damages the central nervous system [27,105]. After high doses of radiation, some specific receptors such as the NMDA receptor and AMP receptor are over activated. "Excitotoxins" such as NMDA and kainic acid, which bind to these receptors, as well as pathologically high levels of glutamate, can cause excitotoxicity, by allowing high levels of calcium ions to enter the cell. Ca^{++} influx into cells activates a number of enzymes, including phospholipases, endonucleases, and proteases such as calpain. These enzymes go on to damage cell structures e.g. components of the cytoskeleton, membranes, and DNA. Excitotoxicity may be involved in stroke, traumatic brain injury and neurodegenerative diseases of the central nervous system (CNS) such as multiple sclerosis, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), fibromyalgia, Parkinson's disease, and Huntington's disease.[27, 105]. It therefore seems logical that excitotoxicity possibly plays a prominent role in CNS injury.

We also postulate that specific Radiation Neurotoxins damage cerebral blood vessels and can induce activation of specific neurotransmitters which may produce exitotoxicity and its consequences [100, 103, 104]. The general toxicity of different types of ionizing radiation is associated mainly with a formation of Specific Radiation Toxins - a group of Radiation Toxins (RT) - Specific Radiation Determinants (SRD). [100, 103, 104]. Radiation toxins concentrate initially in intercellular fluid then disperse into blood and lymph and thereby induce development of systemic injury of hematologic and lymphatic systems. The toxicity of RT SRD subsequently distributes to the cerebrovascular, cardiovascular, and gastrointestinal systems, depending on the magnitude o the exposure. The injury to

cellular components of radiosensitive and pluripotent hematopoietic and other stem cells are induced by processes that are specific for different form of ARS. [100, 103, 104]. *Radiation Toxins*: The specific Radiation Toxins (group SRD) are composed from glycoproteins with high enzymatic activity including high proteolytic, lipolytic, carbohydratolytic properties. RT are formed and accumulated in mammalian cells and migrate into blood and lymphatic circulation in the first hours after irradiation. Radiation Toxins, for the most part, are glycoproteins, pro-enzymes which are activated after relatively high doses of irradiation, i.e. after some radiation threshold for activation is exceeded. This group of glycoproteins has been isolated from cells of irradiated mammalian organisms, and possess the ability to induce inflammatory reactions, apoptosis, and necrosis similar to reactions mediated by radiation itself. The molecular weight of RT (SRD-group) range from 200-250 kDa. The SRD molecules have been isolated from blood, lymph and cells of irradiated animals but lymph has the highest concentrations measured. Irradiated animals develop the different forms of Acute Radiation Syndromes such as Cerebrovascular ARS, Cardiovascular ARS, Gastrointestinal ARS, depending on the level of radiation they were exposed to.

| Acute Radiation Syndromes | Type of Radiation Toxins | Grade ARS Mild | Grade ARS Moderate | Grade ARS Severe | Grade ARS Extremely Severe |
|-------------------------------|--------------------------|----------------|--------------------|------------------|----------------------------|
| Cerebral form of ARS | cerebro-vascular R.T. | SRD-1.1 | SRD-1.2 | SRD-1.3 | SRD-1.4 |
| Cardio-vascular form of ARS | cardio-vascular R.T. | SRD-2.1 | SRD-2.2 | SRD-2.3 | SRD-2.4 |
| Gastro-intestinal form of ARS | gastro-intestinal R.T. | SRD-3.1 | SRD-3.2 | SRD-3.3 | SRD-3.4 |
| Hematological form of ARS | hemato-poietic R.T. | SRD-4.1 | SRD-4.2 | SRD-4.3 | SRD-4.4 |

Table 1. Classification of radiation toxins (SRD group): Radiation Toxins are composed of toxic substances isolated from lymph of irradiated animals with different forms of Acute Radiation Syndromes.

RT Properties- In our experiments RT were isolated from central lymphatics of irradiated animals with different form of ARS and each of the RT possess differences in their radiomimetic properties. Cerebrovascular RT, and to a lesser extent, cardiovascular RT and gastrointestinal RT are neurotoxins. Hematopoietic RT - are strong hematotoxins. Hematopoietic RT can destroy red blood cells and initiate hemolysis, disrupt the blood clotting system and cause multi-organ degeneration and tissues damages. Hematopoietic RT possess important activity against pluripotent stem cells and blood marrow.

| Component (%) | Toxic substance SRD-1 | Toxic substance SRD -2 | Toxic substance SRD-3 | Toxic substance SRD-4. |
|-----------------|-----------------------|------------------------|-----------------------|------------------------|
| Protein | 44.9 ± 0.05 | 48.2 ± 0.03 | 50.1± 0.09 | 56.2 ± 0.12 |
| Lipid | 40.1± 0.04 | 39.6 ± 0.05 | 38.2± 0.04 | 30.1± 0.09 |
| Carbohydrate | 13.4 ± 0.09 | 11.3 ± 0.07 | 10.2 ± 0,03 | 10.1 ± 0,07 |
| Mineral residue | 1.6 ± 0.07 | 0.9 ± 0.02 | 1.3 ± 0.04 | 3.4± 0.17 |

Table 2. Biochemical composition of the toxic substances comprising Radiation Toxins. (SRD- Specific Radiation Determinants)

2. Material and methods

These studies were conducted at several different research institutions and laboratories listed as follows: Biotechnology Centre of Russian Academy of Science (North Osetia), Kazan All-Union Scientific Research Veterinary, Institute Belarussian Scientific and Research Institute for Radiobiology in Gomel, the St. Petersburg Veterinary Institute, the Advanced Medical Technology and Systems Inc., Ottawa-Richmond Hill, Ontario, Canada. The studies were approved by the Animal Care and Use Committee for ethical animal research equivalent, at each institution. A largest volume of purified Radiation Toxin was prepared from larger mammalian irradiated animals. Subsequently the RT were characterized chemically and biologically. The experimental design of later studies compared relative toxicity, potential for development of acute radiation syndromes, and potential lethality after intravenous or intramuscular injections of SRD containing Radiation Toxins. More recent studies focused on the immunogenicity of small doses of SRDs and the potential to use these agents as vaccine countermeasures against radiation injury.

2.1 Experimental animals

These experiments have employed a wide variety of experimental and agricultural animals which include : Black motley cattle, 2.5-3.0 years of age, live weight of 300-350 kg (n=134); Ukrainian pigs, 0.5-1.0 years of age, live weight 35-90 kg (n=142); "prekos" sheep, 3-12 months old, live weight 18-23 kg (n=156); mixed breed (mongrel) dogs, 2-4 years of age, live weight 6.0-6,5 kg (n=162), Chinchilla rabbits, 11-12 months old, live weight 3.5-3.7 (n=180), Latvian draft horses, 3-8 years of age, live weight 350-550 kg (n=32), Balb mice, 2-3 months old, live weight 20-22 g (n=2636), Wistar rats, 3-4 months old, live weight 180-220 g (n=4002).

In all animals, the pre-experiment blood profiles, body temperature, central venous and lymphatic pressure did not exceed the limits of normal variability, (which had been previously measured for five species of mammals. Throughout the entire period of each experiment, ranging from 1 day to 2 years, the control and experimental animals were maintained under identical conditions of feeding, housing, and care, corresponding to livestock maintenance requirements and standards.

2.2 Electromagnetic radiation exposure

The animals were irradiated in RUM-17, Puma, and Panorama devices. The dose rate varied from 30Gy to 100Gy

2.3 Experimental design

Four independent experiments were performed with administration (IV or IM) of Radiation Toxins (SRD RT) to healthy, radiation naive animals that induced development of clinical symptoms of the Acute Radiation Syndromes. The administration of injection of the toxin was administered into veins (IV), into a muscle (IM), into the abdomen (IP) or into the skin (SC).

Experiment N1. Administration of Cerebrovascular form of Radiation Toxins to radiation naive animals in doses 0.1 mg/kg; 0,5 mg/kg; 1 mg/kg; 2 mg/kg; 3 mg/kg up to 30 mg/kg initiates development of specific toxic reactions with symptoms mimicking the cerebral form of ARS. Injection of Cerebrovascular Radiation Toxins (SRD-1) in excess of 3 mg/kg doses to rats, rabbits, sheep resulted in lethality.

Experiment N2. Administration of radiation toxins of Cardiovascular Radiation Toxins (SRD-2) to radiation naive animals in doses 0.1 mg/kg; 0,5 mg/kg; 1 mg/kg; 2 mg/kg; 3 mg/kg up to 30 mg/kg produced specific toxic reactions with symptoms mimicking the Cardiovascular form of ARS.

Experiment N3. Administration of Gastrointestinal Radiation Toxins (SRD-3) group to radiation naive animals in doses 0.1 mg/kg; 0,5 mg/kg; 1 mg/kg; 2 mg/kg; 3 mg/kg up to 30 mg/kg produced development of specific toxic reactions with symptoms mimicking the GI form of ARS.

Experiment N4. Administration of Haemotopoietic Radiation Toxins (SRD-4) to radiation naive animals in doses 0.1 mg/kg; 0,5 mg/kg; 1 mg/kg; 2 mg/kg; 3 mg/kg up to 30 mg/kg produced specific toxic reactions with symptoms of the hematological form of ARS.

2.4 Radiation toxins description and isolation

The methods of immune depletion, affine immuno-lympho-plasmasorption, as well as direct extraction were used to refine and purify the specific Radiation Toxins from the central lymph of animals with Cerebrovascular, Cardiovascular, Gastrointestinal and Haemotopoietic forms of Radiation Toxins.[104, 110]

Specific Radiation Determinants (SRD)- a group of Radiation Toxins isolated from lymph of irradiated mammals, had been divided to four important groups: 1.Cerebrovascular neurotoxic RT (SRD-1); 2.Cardiovascular RT(SRD-2); 3.Gastrointestinal RT (SRD-3); 4.Hematopoietic RT (SRD-4). The radiomimetic properties of Radiation Toxins preparations were evaluated on the basis of their capacity to induce radiobiological effects in radiation-naive animals after they were administered parenterally. Specific Cerebrovascular, Cardiovascular, Gastrointestinal and Hematopoietic Toxins (isolated from the lymph of animals irradiated at doses inducing Cerebral, Cardiovascular, Gastrointestinal and Haemotopoietic clinical forms of ARS) were dissolved in an isotonic solution of NaCl. The doses of preparations of Radiation Toxins which were administered was based on computation of the amount of SRD per unit volume of central lymph and absorbed dose of radiation. Radiation toxins of SRD group possess highly toxic properties and induce neuro-vascular and hematotoxic reactions in short time after administration.

Neurotoxins of SRD-1 group isolated from L.S. (lymphatic system) of irradiated animals with Cerebrovascular ARS after intra-muscular or intra-venous single injection in doses 5 mg/kg, 10 mg/kg, 15 mg / kg, 30 mg/kg activate acute neuro-vascular reactions with signs of injury of central and peripheral nervous system and damage of vascular walls of central nervous system.

Neurotoxins of SRD-2 group isolated from L.S. of irradiated animals with cardio-vascular form of ARS after intra-muscular or intra-venous single injection in doses 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg activate acute cardio-vascular and neuro-vascular reactions with signs of injury of central and peripheral vascular system. Neurotoxins of SRD-3 group isolated from L.S. of irradiated animals with gastro-intestinal form of ARS after intra-muscular or intra-venous single injection in doses 5 mg/kg, 10 mg/kg, 15 mg/kg and 30 mg/kg induce acute gastrointestinal syndrome with signs of injury of vascular system of gastro-intestinal system and injury of epithelium of intestinal walls. Hematotoxin of SRD-4 isolated from L.S. of irradiated animals with Hematopoetic form of ARS after single dose injection with doses 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg activate hematotoxic reactions with activation red blood cells and white blood cell lysis and activation of apoptosis of hematopoietic cells progenitors.

3. Results

SRD-1 Radiation Toxins induced injury of Central Nervous System and development of Acute Cerebrovascular form of Radiation Syndrome

The Cerebrovascular form of Radiation Toxins (SRD-1) were administered to radiation naïve animals in doses of 0.1 mg/kg; 0.5 mg/kg; 1 mg/kg; 2 mg/kg; 3 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg and 30 mg/kg. The injection of Cerebrovascular Radiation Toxins (SRD-1) to rats, rabbits, sheep produced bioeffects similar to the cerebrovascular form of ARS. (see Table 3) After parenteral administration, the animals experienced a short period of extreme agitation, followed by a deep coma, with alterations in breathing patterns and subsequently cardiovascular collapse. The results of autopsy of their bodies demonstrated cerebral hemorrhagic strokes, cerebrospinal fluid with blood (reddish color), hemorrhagic lesions in brain tissue. Internal organs were filled with blood. Multiple petechiae were observed on serous membranes. Depending on doses of cerebrovascular Radiation Neurotoxins, death was registered in 15 min or up to 5 hours after injection.

Case #1: The species studied in the experiment- 4 month old lambs. Radiation neurotoxin (SRD-1) in single dose of 5 mg/kg of weight was administered intramuscularly to radiation-naïve sheep. The injected animals were dead within 20 minutes after injection, with a profound clinical picture of cerebrovascular ARS, Within 5 minutes there was central nervous excitation and nervousness, and within 15 minutes there were signs of coma, followed by death. Post-mortem histopathology revealed: Brain- red discoloration of cerebrospinal fluid (CSF) with inflammatory meninges; multiple petechiae and hemorrhage on meninges surfaces. Grey matter of the brain - hemorrhages. Liver- dark-red coloration, with multiple petechiae and hemorrhages. Kidneys- multiple petechiae and hemorrhages. Clinical Diagnosis: Acute Cerebrovascular Shock / Acute Cerebrovascular form of ARS induced by single injection of radiation neurotoxin

| Radiation Toxins | Symptoms | Toxic doses 5mg/kg | Toxic doses 10mg/kg | Toxic doses 15mg/kg | Toxic doses 30 mg/kg |
|--|--|---------------------------|------------------------|--------------------------|-------------------------|
| Cerebrovascular Neurotoxin SRD-1. | Cerebral edema, hemorrhagic stroke | Death in one -three hours | Death in one hour | Death in 15-30 min | Death in 15 min |
| Cardiovascular SRD-2. | Cardiac insufficiency, hemorrhagic stroke. | Death in three days | Death in 14 hours | Death in 7 hours | Death in 2 hours |
| Gastro-Intestinal SRD-3. | Vomiting, diarrhea, hematochezia and melana. | Death in 10-15 days | Death in 5-7 days | Death in 2-3 days | Death in 24 hours |
| Hematopoietic SRD-4 | Peripheral edema, ecchymosis, anemia, granulocytopenic fevers. | Death in 2-4 weeks. | Death in next 10 days. | Death in next 7-10 days. | Death in next 4-5 days. |
| Mixture of lower doses of toxins SRD 1+2+3+4 | Cerebral edema, vomiting, hemorrhage, cardiac insufficiency. | Death in 4-5 hours | Death in 1-3 hours | Death in one hour | Death in one hour |

Table 3. Radiation Toxins: Toxic properties of Radiation Toxins (SRD Group 1-4) after single injection and different forms of Acute Radiation Syndromes induced by each.

SRD-2 Radiation Toxins induced injury of the Cardiovascular System and development of symptoms mimicking the Acute Cardiovascular Radiation Syndrome

The Cardiovascular form of Radiation Toxins were administered to radiation naive animals in doses of 0.1 mg/kg; 0,5 mg/kg; 1 mg/kg; 2 mg/kg; 3 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg and 30 mg/kg. The injection of Cardiovascular (SRD-2) RT in toxic doses to rats, rabbits, sheep produced symptoms similar to the cardiovascular form of ARS. (see Table 3) In this experiment, the following symptoms were observed: a delayed, shorter duration and less extreme period of agitation than with SRD-1 RTs, followed by tachycardia, cardiac arrhythmias, tachypnea. Postmortem histopathological analysis revealed inflammatory changes in the cardiac muscle tissue.

Case #2: Species in experiment- 4 months old lamb. Radiation neurotoxin (SRD-2) in single dose 5 mg/kg of weight was administered intravenously. 14 hours after injection all the injected lambs were dead after with a clinical picture of cardiovascular shock: agitation, fever, agitation, tachycardia, arrhythmias, hypotension, hyperventilation, followed by lethargy, signs of coma and death. Post-mortal histopathology showed: Heart- damaged microvasculature, cardiac vasoconstriction , ischemic myocardium, contraction band necrosis, multiple cardiac hemorrhages. Kidneys: multiple petechies of haemorrhages, acute tubular necrosis and renal failure.

SRD-3 Radiation Toxins induced injury of the Gastrointestinal System and development of symptoms mimicking the Acute Gastrointestinal Radiation Syndrome

Administration of Gastrointestinal Radiation Toxins (SRD-3) were administered to radiation naive animals in doses of 0.1 mg/kg; 0,5 mg/kg; 1 mg/kg; 2 mg/kg; 3 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg and 30 mg/kg. Injection of SRD-3 in toxic doses to experimental animals produced different grades of the Gastrointestinal form of ARS. (see Table 3) Case #3: Experimental species: one year old sheep. After a single dose injection of 15 mg/kg of the SRD-3 Gastrointestinal radiation toxins (isolated from central lymph of animals with the gastrointestinal form of ARS) intravenously, the animals elicit the following: Clinical signs-decrease in appetite and increased peristalsis within hours after injection, followed by severe diarrhea, hematochezia, dehydration, and later followed by collapse over several days. Death occurred 5-10 days after toxin administration. Histopathology revealed- local vasoconstriction, damaged microvasculature, large vessel vasodilatation and hyperemia of the small bowel and colon. Hypertension was manifested approximately two hours after intravenous injection. Ultimately hypotension developed after days of vomiting, diarrhea and dehydration.

SRD-4 Radiation Toxins induced development of Acute Hematopoietic Acute Radiation Syndrome

The Hematopoietic Radiation Toxins (SRD-4) were administered to radiation naive animals in doses of 0.1 mg/kg; 0,5 mg/kg; 1 mg/kg; 2 mg/kg; 3 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg and 30 mg/kg. Injection of SRD-4 to experimental animals resulted in erythrocytopenia, lymphocytopenia, leukocytopenia, and thrombocytopenia within days to weeks after injection. (see Table 3) The development of clinical features of the Acute Hematopoietic Syndrome depended on the dose of SRD-4 Hematopoietic Radiation Toxins injected to radiation naïve animals. Autopsy of those animals that died showed acute or chronic hematotoxic reactions. The clinical signs were: short-term agitation within 2 hours after administration accompanied by a short-term leukocytosis which gave way to a progressive, profound leukopenia, mainly attributable to a decrease in the absolute number of lymphocytes, the minimal levels of which were measured between days 7 and 15 after injection. Total WBC was 1.2-1.6 1000/ μ l to 0.4-0.5 thousand/ μ l in sheep and 1.8-2.5 thousand/ μ l to 0.5-0.7 thousand/ μ l in cattle. The recovery of absolute and relative levels of leukocytes and lymphocytes was observed in some animals between days 30 and 60. Blood counts exhibited thrombocytopenia accompanied by progressive erythrocytopenia, which developed into profound anemia. An extensive blood analysis of the peripheral blood of the cattle showed that the processes induced by the SRD-4 injection and the processes occurring after irradiation were nearly identical. Analysis of the clinical reaction to SRD-4 administration, which was assessed on the basis of body temperature, and heart and respiration rate, established that all experimental animals showed reactions of the same type for all the tested doses and that sheep and horses were more sensitive to the administered preparation. Thus, in sheep, which received SRD-4 at the maximum dose tested, the body temperature increased by 1.5-2 ° C, reaching 41.2° 1 or 2 days before death. This core body temperature increase was accompanied by severe tachycardia and tachypnea, which were measured at 105-106/min. and 70-80/ minute, respectively. When SRD-4 was administered in the intermediate and maximum dose levels, both sheep and cattle showed changes of the same type but of lesser degree depending on the dose. The majority of experimental animals recovered between days 30-60 after injection of the preparation. Post-mortem examination of the animals that died showed changes characteristic of acute radiation

sickness, accompanied by marked hemorrhage. Death often will occur secondary to overwhelming bacterial or fungal sepsis. Some sheep showed areas of skin epilation on the back and abdomen.

Case# 4. Species- sheep. Hematoxin, SDR-4, isolated from irradiated mammals with the Hematopoietic form of ARS, was injected via single dose to non-irradiated mammals. The SRD-4 RT induced significant changes in white blood cells (WBC) and red cells profile (RBC). Hematoxin injected to non-irradiated sheep in doses 5 mg/kg, 10 mg/kg, 30 mg/kg activated a complex reaction which included general inflammation, vascular endothelial cell injury, apoptosis and necrosis of blood progenitor/ stem cells. The levels of sheep erythrocytes, leukocytes, lymphocytes, thrombocytes significantly increased in first hours and day after single injection of radiation hematotoxin and could be a result of general inflammation reactions and stimulation of immune system. However the levels of erythrocytes, leukocytes, lymphocytes, thrombocytes significantly decreased after 72 hours after hematoxin administration and the minimal level of erythrocytes, leukocytes, lymphocytes were measured after 168- 360 hours following a single dose injection of the radiation-induced hematoxin. (see Tables 4- 7) Characteristics of the peripheral blood of large horn cattle after a single injection of Hematopoetic Radiation Toxin (SRD-4) were measured and levels of erythrocytes, leukocytes, lymphocytes significantly increased in first hours after a single dose injection of radiation hematotoxin and decreased after 72, 168, and 360 hours after administration. (see Tables 8- 11)

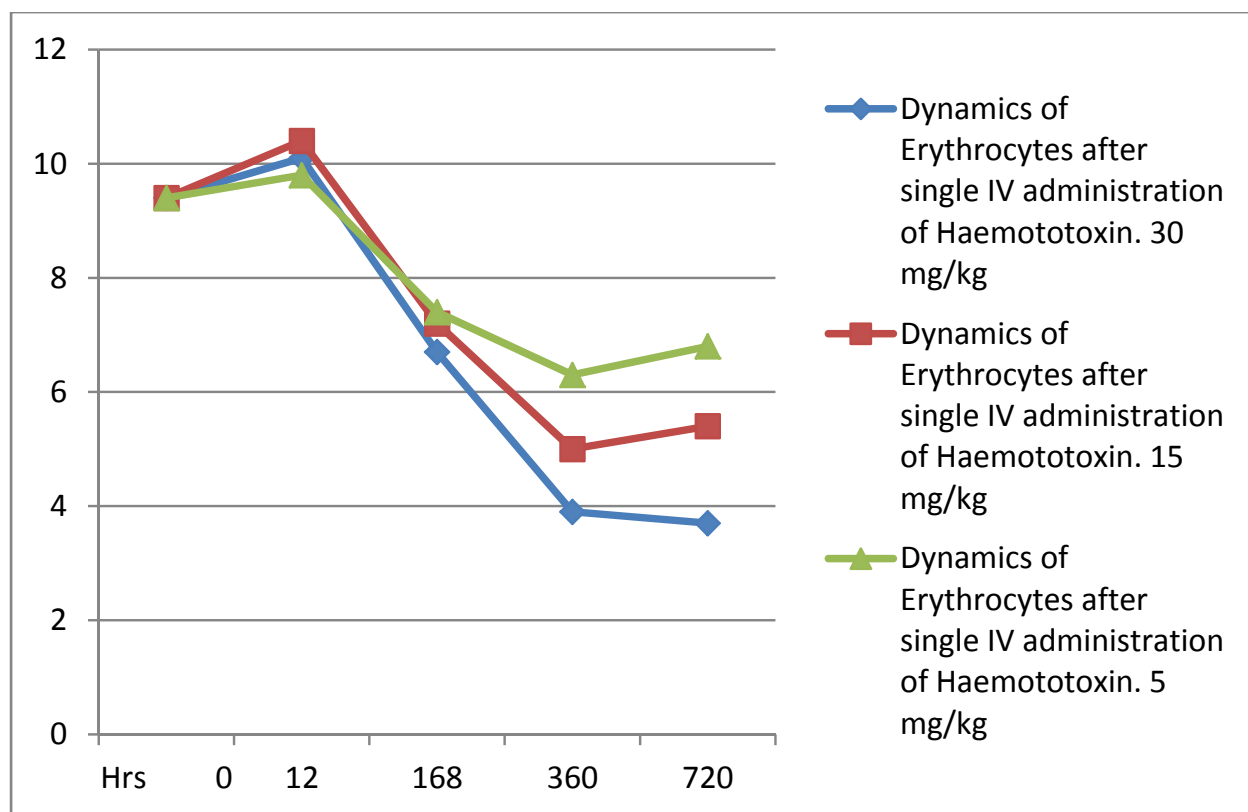


Fig. 1. Dose-dependent changes in sheep peripheral blood erythrocytes after a single injection of Hematopoetic Radiation Toxin (SRD-4).

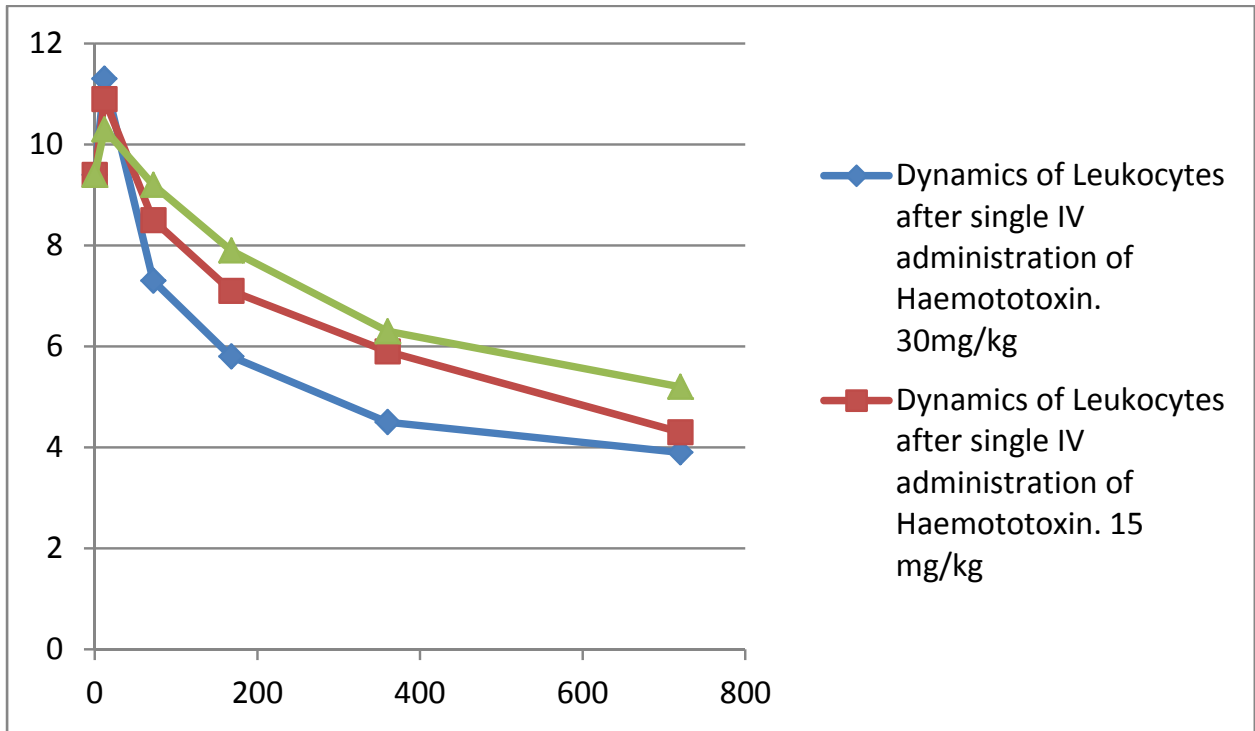


Fig. 2. Dose-dependent changes sheep peripheral blood leukocytes after a single injection of Hematopoietic Radiation Toxin (SRD-4).

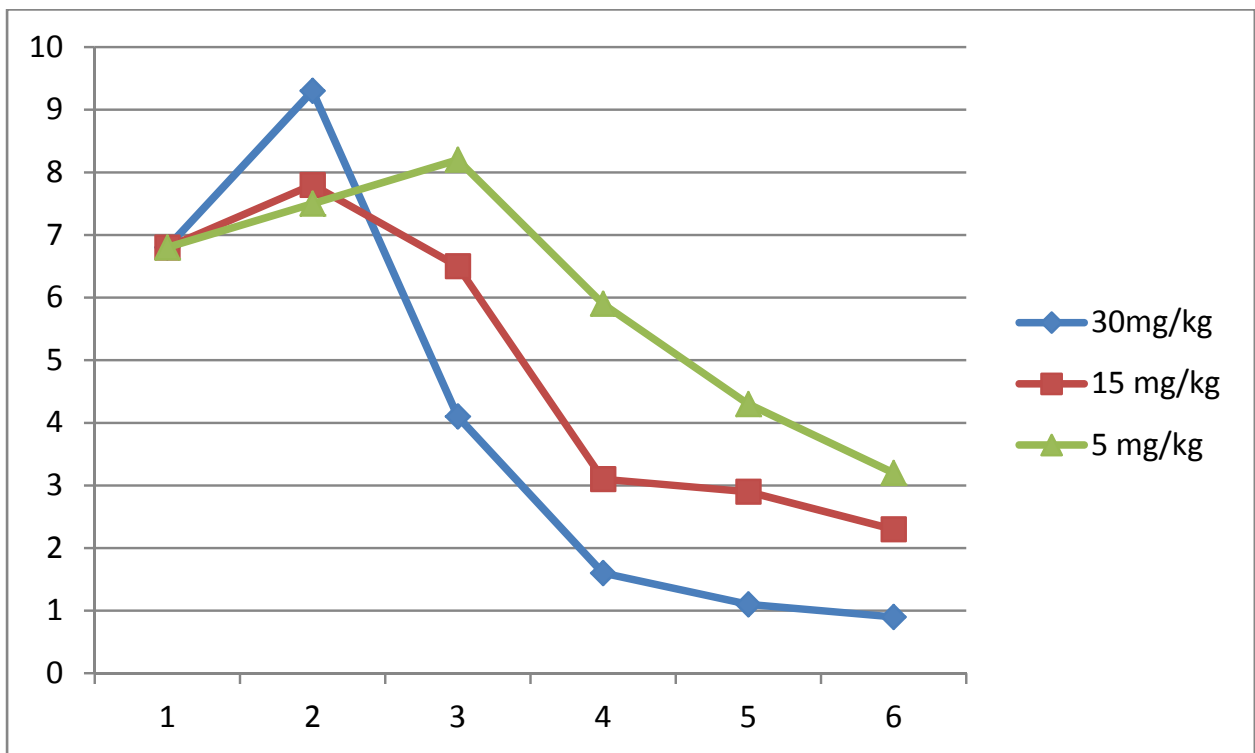


Fig. 3. Dose-dependent dynamics of sheep Lymphocytes after single IV administration of Hematotoxin (SRD-4).

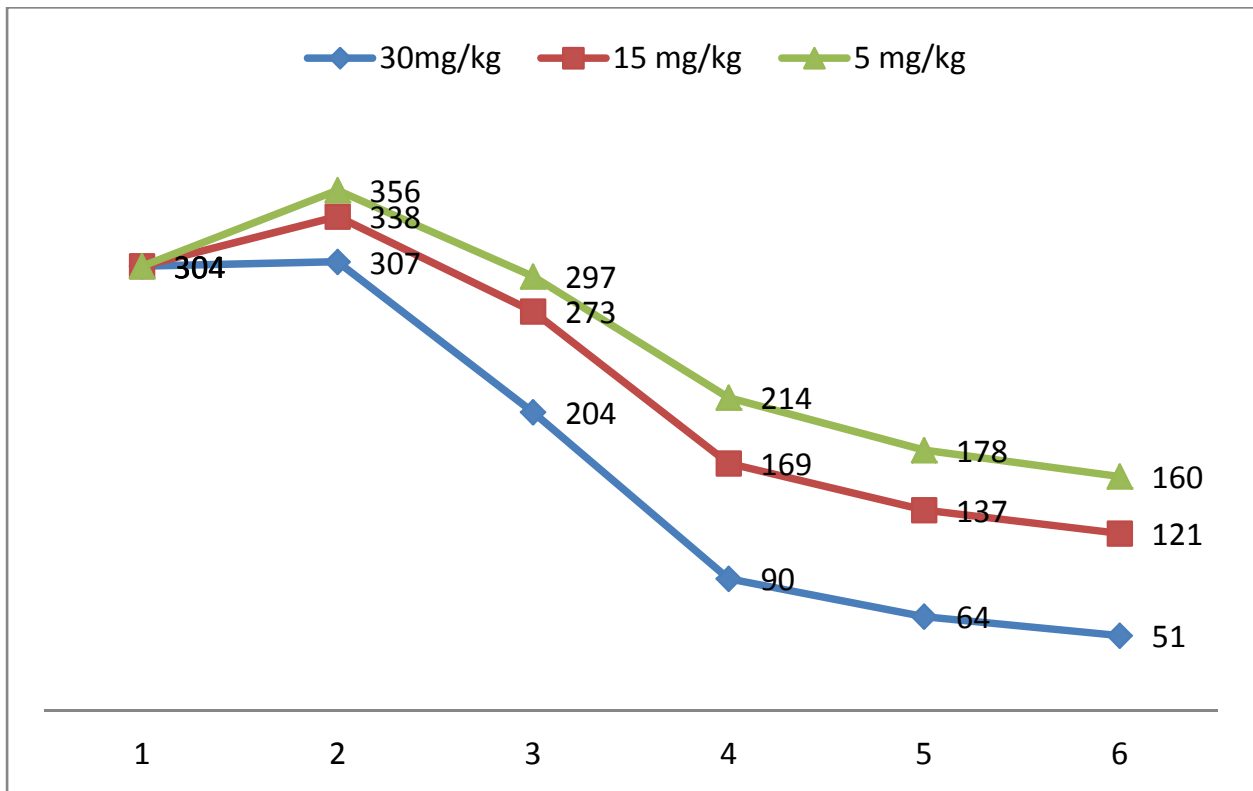


Fig. 4. Dose-dependent dynamics of sheep thrombocytes (platelets) after single IV administration of Hematotoxin (SRD-4).

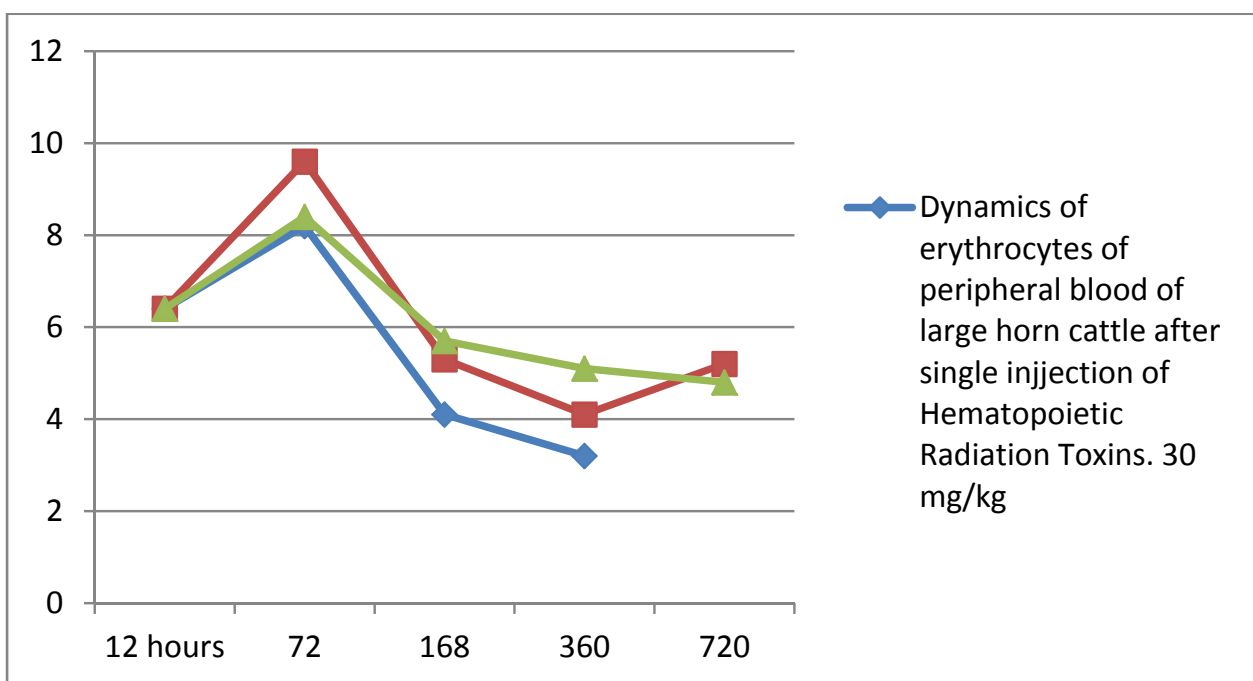


Fig. 5. Dose-dependent characteristics of large horn cattle peripheral blood erythrocytes after single injection of Hematopoietic Radiation Toxin (SRD-4).

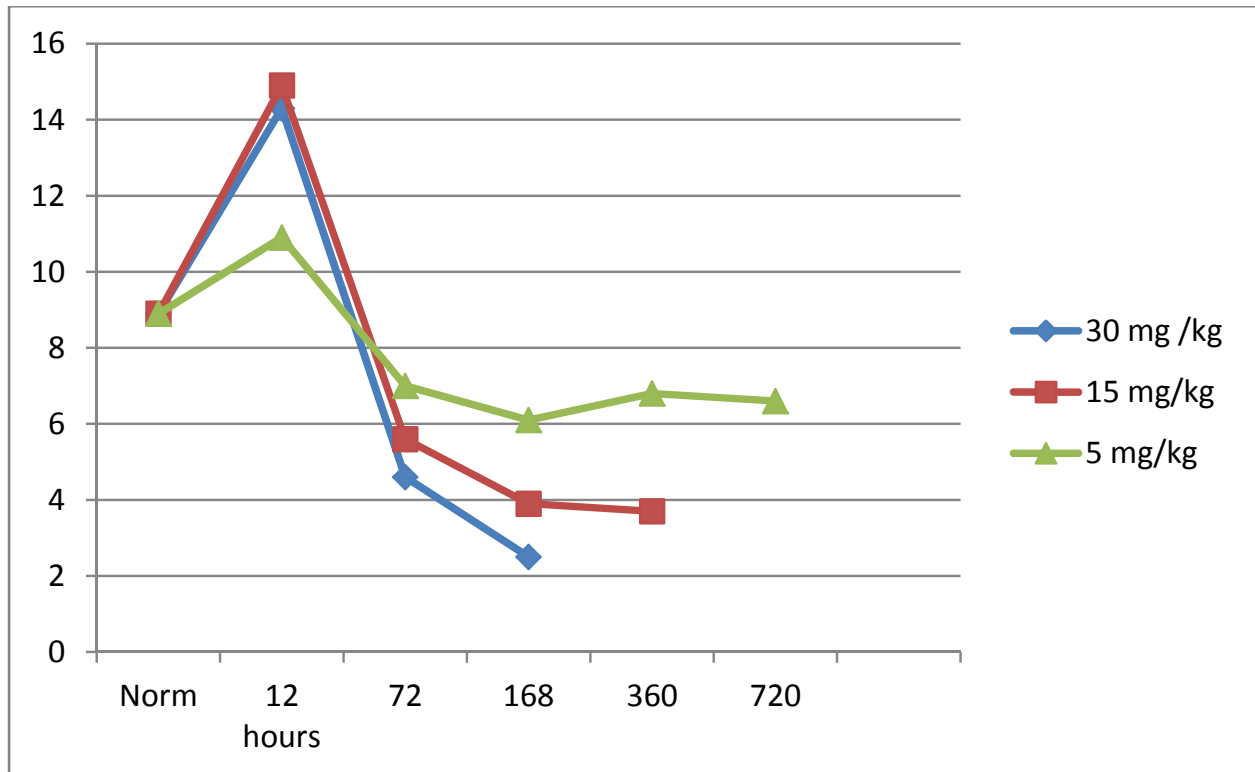


Fig. 6. Dose-dependent changes in cattle peripheral blood leukocytes after a single injection of Hematopoietic Radiation Toxin (SRD-4).

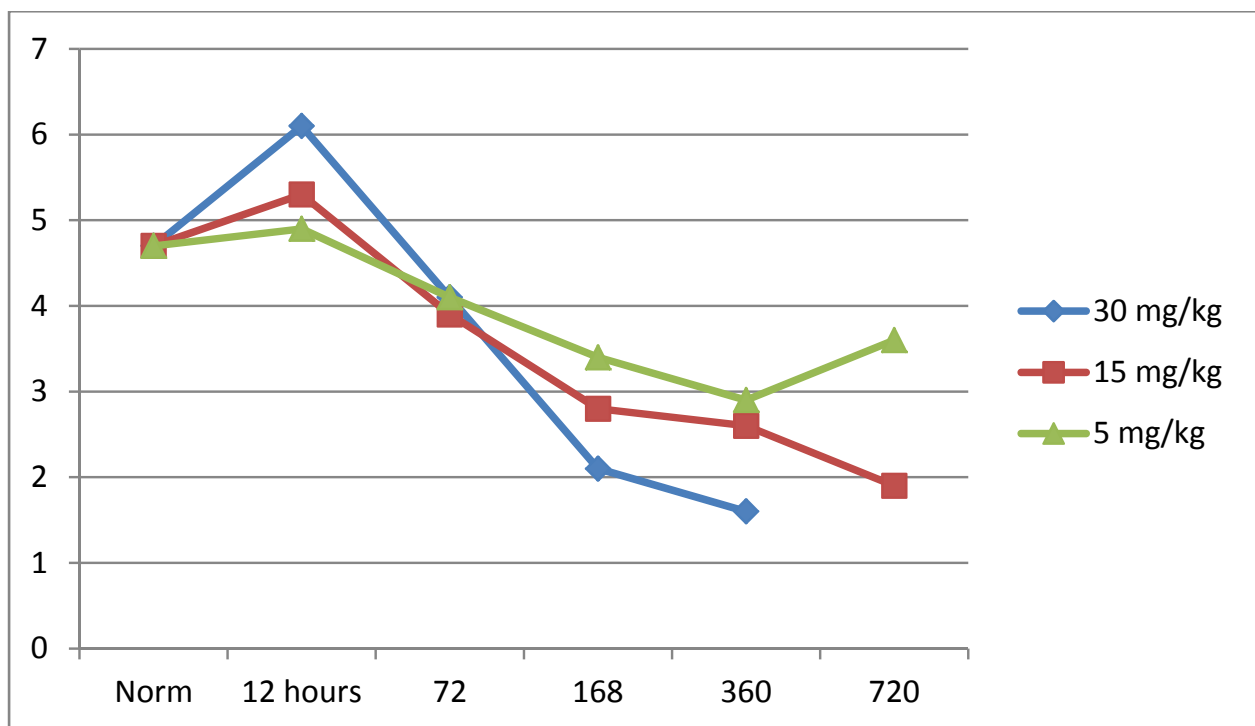


Fig. 7. Dose-dependent dynamics of cattle Lymphocytes after single IV administration of Hematotoxin (SRD-4).

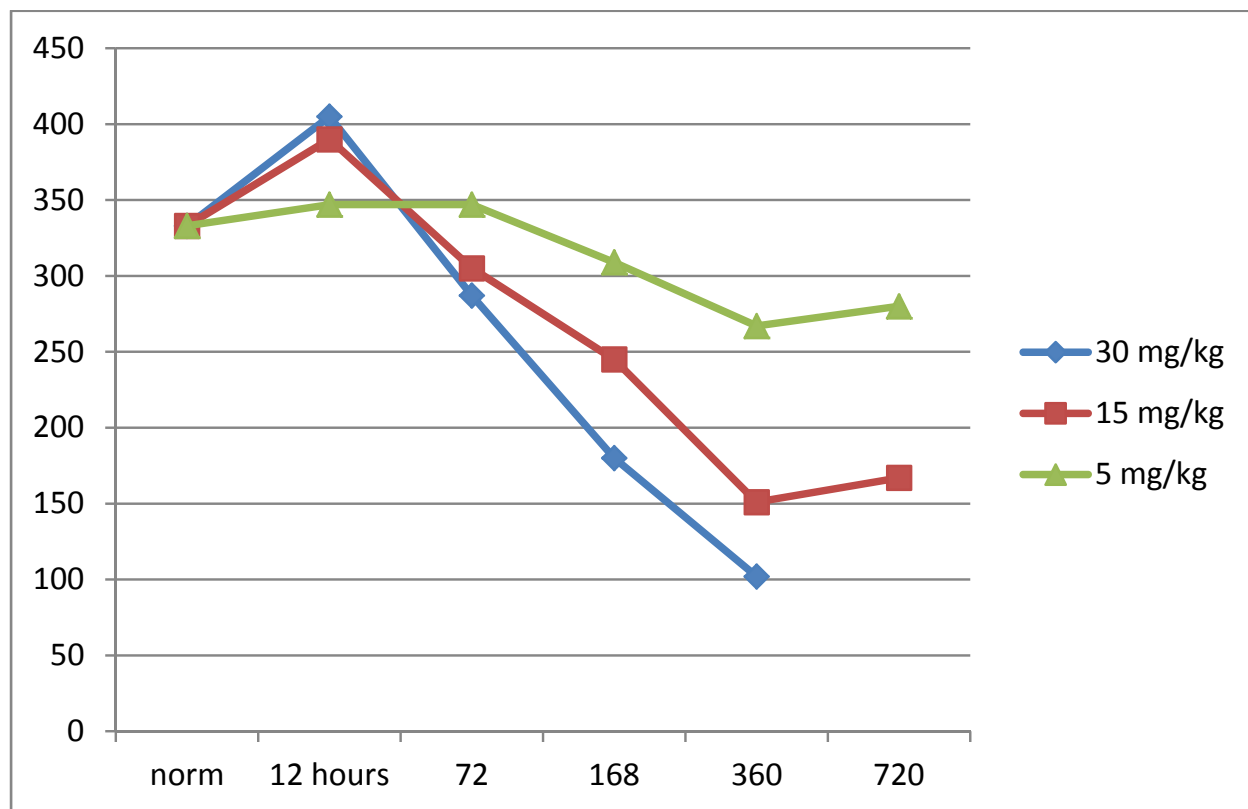


Fig. 8. Dose-dependent dynamics of cattle thrombocytes (platelets) after single IV administration of Hematotoxin (SRD-4).

4. Discussion

Radiation toxin SRD-1 (cerebrovascular radio-neurotoxin) activates pathophysiological processes and clinical symptoms / signs of central and peripheral nervous system injury with development of neurological and cognitive deficit, activation, followed by depression, of specific centers of the central nervous system, including autonomic nervous system pathways.

Radiation toxin SRD-2 (cardiovascular radiotoxin) activates pathophysiological processes and clinical symptoms / signs of cardiac and vascular inflammation and injury with endothelium cell, microvascular vessel and cardiovascular system tissue showing apoptosis and necrosis. Severe hypotension and tachycardia were important clinical indicators of cardiovascular acute radiation syndromes with the subsequent development of cardiac myocyte necrosis.

Radiation toxin SRD-3 (gastrointestinal radiotoxin) initiates symptoms signs of gastrointestinal system injury including anorexia and vomiting, induced by the toxic effects and damage to the vascular and lymphatic vessel network of the gastrointestinal system, as well as apoptosis of intestinal lining epithelial cells, including crypt / villi necrosis. Severe diarrhea and melena / hematochezia were important clinical indicators of the mimicked gastrointestinal acute radiation syndrome.

Radiation toxin SRD-4 (hematotoxin) induces development of red cell lysis and apoptosis of white blood cell and red cell progenitors. The action of the SRD-4 hematotoxin is described

in Tables 4-7 for sheep and 8-11 for cattle. Thrombocytopenia, lymphocytopenia, granulocytopenia, ecchymosis, hemorrhage and coagulopathy were important clinical signs of the mimicked hematopoietic acute radiation syndrome.

Other clinical indicators of the Radiation Toxins (RT) included cutaneous system involvement: including: cutaneous edemas, blistering, desquamation, hair loss, ulcer and necrosis.

Severe Acute Radiation Exposure syndromes will induce Toxic Multiple Organ Failure (TMOF) and Toxic Multiple Organ Involvement (TMOI) - e.g. pneumonitis, renal failure, renal hypo-perfusion, acute tubular necrosis, hepatic failure, etc. as an acute consequences of radiation toxemia. Similarly, bacterial toxemia induced by bacterial superantigens and radiation-induced toxemia are very similar in their clinical manifestation and similar in their pathophysiological actions. In a related matter, the molecular structure of radiation antigens (toxins) and bacterial superantigens, as well as different snake venom toxins have similarities.

Thus, if a researcher administers specific Radiation Toxins of one of the SRD groups to radiation naive animals, toxicity will be observed along a dose response curve, from doses as small as 0.1 mg/kg or 0.5 mg/kg up to the highest tested dose of 30 mg/kg. The observed toxicity will mimic the ARS syndrome specific to the exposure of the animals from which the SRDs were acquired. Thus the exogenously administered SRD initiates development of specific toxic reactions with symptoms of a specific ARS, hence the name-specific radiation determinant (SRD 1-4). The SRD-group molecules possess both toxic and antigenic properties. The molecular Koch's postulates, which are commonly applied to bacterial toxin pathogenicity, could also be applied to the biological effect produced by Radiation Toxins, and those postulates would mostly be satisfied to list RT as the causative agents [101, 106].

4.1 Comparative analysis of bacterial toxins vs radiation toxins (see table 12)

We compared lethal toxicity and clinicopathological features and characteristics for Radiation Toxins and Bacterial Toxins. Pathogenic bacteria which colonize the intestine, can invade intestinal epithelial cells and lymphatics, and/or produce one or more toxins that are important etiologies of diarrheal disease [32, 42, 48, 57, 86, 87, 88]. Bacteria produce toxins and the mechanisms of action of bacterial toxins can be classified into three important groups (see Table 12) : 1. Toxins with intrinsic enzymatic activity - cytotoxic bacterial toxins. 2. Toxins that binds to receptors that stimulate the actions of second messengers - cytotoxic bacterial toxins (e.g. botulinum or cholera toxins) . 3. Toxins that damage eukaryotic cell membranes - membranotoxic bacterial toxins. [32, 42, 48, 57, 86,]. We postulate that radiation toxins possess high enzymatic activity, damage cell membranes, and also activate cell receptors. We postulate that radiation toxin mechanisms of action depend on the toxin type and dose of radiation toxins. We postulate that Radiation Toxins could initiate two different types of cell death - programmed (apoptosis) or necrosis. [90,91].

Escherichia Coli is an Enteric Gram-negative rods and their pathogenic strains contained the wide group of toxins with different properties. Escherichia Coli contain endotoxin - lipopolysaccharide, which is antigenic and virulence factor. [12, 48]. Escherichia Coli contains three groups of antigens - O, H and K. The O antigens - cell wall antigens - found in polysaccharide portion of LPS. The H antigens are associated with flagella and the K antigens are associated with the fimbriae or capsule. [12,48,78,79,87,88]. Enteroaggregative E.Coli - EAEC, produce three important toxins. EAEC heat stable enterotoxin is a 4.1-kDa protein. The

other EAEC heat -labile enterotoxin with molecular weight 120 kDa. The third EAEC enterotoxin is a heat labile, 108 kDa protein with the ability to induce a severe acute intestinal inflammation. [12,78,79,87]. Enterohemorrhagic Escherichia coli, EHEC contains a Shigella-like toxin. The Shiga toxin family contains Shiga-like toxin 1 (SLT-1) and Shiga-like toxin 2 (SLT-2). EHEC strains produce SLT -2 or combination SLT 1 and SLT 2 [12]. Shiga toxin is a cytotoxic for endothelial and epithelial cells including human colonic and ileal epithelial cells, and B-lymphocytes [12]. Enteropathogenic Escherichia coli induce an important and distinctive histopathologic lesion in the intestine with destruction of microvilli – the classic histopathologic lesion - AE lesion [12]. There are two proteins responsible for development AE lesion – a 94-kDa protein and protein encoded by the eaeB gene. [12,78,79].

| Toxins | Mechanism of Action | Symptoms |
|--------------------------------------|---|---|
| 1. Enterotoxigenic E. Coli (ETEC). | 1. ETEC - Three toxins: EA- ST, EA- HL, EA-HL | ETEC toxins induce hypersecretion by intestinal mucosa cells, watery diarrhea |
| 2. Enteropathogenic E. Coli (EPEC). | 2. EPEC - Shiga-like toxins. | EPEC toxins causing destruction of microvilli and development focal lesions. |
| 3. Enterohemorrhagic E. Coli (EHEC). | 3. EHEC - verotoxin or Shiga-like toxin. | EHEC induce severe form of hemorrhagic colitis, acute renal failure or hemolytic uremic syndrome. |
| 4. Enteroinvasive E. Coli (EIEC). | | EIEC induce dysentery like syndrome |
| 5. Enteroadherent E. Coli (EAEC). | | EAEC cause traveler' diarrhea |

Table 4. Bacterial Toxins and their mechanisms of action.

Enterotoxigenic Escherichia coli produce heat – stable (ST) and heat-labile enterotoxins (LT). STa is a cysteine-rich, 18-amino-acid peptide. ST is produced as a precursor that is cleaved by signal peptidase and translocated to the periplasm where is added three intra-molecular disulfide bonds crucial for toxin activity. A second proteolytic agent occurs extracellularly and produce biologically active and toxic ST [12,81,]. STa acts by binding to a protein intestinal epithelial receptor localized in brush border membrane. [12,78].

E.coli heat-stable enterotoxin b is a 71-amino-acid precursor protein secreted extracellularly and proteolytically processed to a toxic form as a 48-amino-acid protein [12, 79]. E. coli heat-labile enterotoxin I is closely related to CT, including its structure and enzymatic activity. [12]. Other Escherichia coli Toxins include Cytolethal distending toxin and Cytotoxic necrotizing factors [12, 78,79].

Staphylococcus aureus produces serologically distinct protein exotoxins named A, B, C1, C3, D, E. All of these exotoxins are small proteins (24-30 kDa) with important biological activities. All seven toxins stimulate local receptors in upper intestinal tracts [12, 86]. Staphylococcal enterotoxins are likely playing an important role in cytokine production and are most potent T-cell receptor activators and inducers of lymphocyte proliferation. This class of toxins could be classified as “superantigens”, as well as the toxins produced by Streptococcus spp. and Clostridium perfringens. Superantigens presented directly to the T-

| Clinical symptoms induced by Bacterial Superantigene | Clinical symptoms induced by radiation toxins (SRD group) and by irradiation. |
|---|---|
| Central Nervous System involvement Peripheral nervous system Confusion, Irritability, Lethargy | CNS involvement: Cerebro-Vascular Acute Radiation Syndrome. Radiation Induced Neurotoxin. Neurological and Cognitive Deficit, Vomiting. Severe form of brain microcirculation disorder. Clinical futures of hemorrhagic stroke. |
| Cardio-Vascular System involvement Systolic Blood Pressure :< 90 mmHg Tachycardia >100 beats/min, Hypotension, Hyperventilation, Loss of Sympathetic responsiveness . | Cardio-Vascular System involvement: Cardio-vascular Radiotoxin-induced Acute Radiation Syndrome.- Tachycardia, Bradycardia, Arrhythmias, Hypertension followed by severe hypotension (Systolic Blood Pressure:< 80 mmHg), hyperventilation. |
| Gastro-Intestinal System Involvement Vomiting, diarrhea, hematochezia and stool mucous (depending on which enteric toxin). | Gastro-intestinal System Involvement: Gastro-Intestinal Acute Radiation Disease. Radiotoxin. Vomiting, diarrhea. Melena and hematochezia. Abdominal pain- moderate to severe. |
| Bacterial Superantigen hematotoxicity Thrombocytopenia, Platelet count < 100,000/ mm ³ .- Thrombocytopenia., leukopenia, pancytopenia. Disseminated Intravascular Coagulation (DIC) Syndrome. | Hematopoietic Toxicity: Acute Radiation Hematopoietic Syndrome. Hematopoietic Radiation Toxin- Thrombocytopenia, Lymphocytopenia, Granulocytopenia. Pancytopenia. |
| Cutaneous involvement: diffuse maculopapular, petechial or ecchymotic rash, intense erythroderma, desquamation (e.g. meningococemia or toxic shock syndrome). | Cutaneous System Involvement: Possible action of any type of Radiation Toxins. Swelling, edema, blistering, desquamation, hair loss, ulceration and skin necrosis |
| Multiple Organ Failure and Multiple Organ Involvement. | Multiple Organ Failure and Multiple Organ Involvement. |
| Renal failure, Renal hypo-perfusion; Oliguria, Acute tubular necrosis | Renal failure, renal hypo-perfusion, Acute tubular necrosis. |
| Hepatic failure and inflammation | Hepatic failure |
| Pulmonary System: Hyperventilation with Respiratory alkalosis, pulmonary hypertension and edema, hypoxemia, ARDS | Pulmonary System: Hyperventilation. Radiation induced pneumonitis and subsequent pneumonia, ARDS. |

Table 5. Comparative analysis of clinical symptoms induced by radiation and/or Radiation Toxins - (SRD group 1-4)- induced ARS and those produced by Toxic Shock Syndrome induced by Bacterial Superantigene.

cell receptors by cells containing major histocompatibility complex class II molecules, without processing by antigen-presenting cells [32,48,86]. Superantigens (SAGs) are a class of antigens which cause non-specific activation of T-cells resulting in polyclonal T cell activation and massive cytokine release. The large number of activated T-cells secrete large amounts of cytokines (the most important of which is TNF-alpha). [32,86]. SAg stimulation of antigen presenting cells and T-cells elicits a response that is mainly inflammatory, focused on the action of TH-1 T-helper cells. Some of the major products are IL-1, IL-2, IL-6, TNF- α , gamma interferon (IFN- γ), macrophage inflammatory protein 1 α (MIP-1 α), MIP-1 β , and also monocyte chemoattractant protein 1(MCP-1). Clinical symptoms / signs induced by bacterial Superantigenes include central and peripheral nervous system involvement (confusion, lethargy, vomiting, anorexia), involvement of the cardiovascular system with development of hypotension, tachycardia and loss of sympathetic responsiveness. Bacterial Superantigenes activate toxic processes within the gastrointestinal system including acute vomiting and diarrhea. The important signs and clinical picture of bacterial superantigen hematotoxicity with development thrombocytopenia, leukopenia, lymphocytopenia and development of coagulopathy. Bacterial Superantigenes could activate injury of cutaneous system and diffuse rash, erythrodermia, desquamation. [32,86] Radiation Toxins of SRD groups 1-4 can activate similar pathological processes, clinical picture and clinical signs as the bacterial superantigen toxicity and the three entities: 1) Acute Radiation Syndromes, 2) SRD RT- induced acute syndromes and Bacterial Toxin- induced septic reaction and toxicity can be compared. (see Table 5)

4.2 Comparative analysis of toxins produced by venom toxins and radiation toxins (see table 6)

Neurotoxic proteins can be isolated from various snake venoms. These proteins can potentially be a mix of neurotoxins, which attack the nervous system; hemotoxins, which attack the circulatory system; plus cytotoxins, bungarotoxins and many other toxins that affect the body in different ways [6,29,49,60,61,82,83,84,85]. Almost all snake venom contains hyaluronidase, an enzyme that ensures rapid diffusion of the venom into the body of the bite-victim [82,84]. Viper venoms from the Elapidae, Hydrophiidae, Atractaspididae, Viperidae and Colubridae families contain at least 25 separate classes of biologically active compounds, including enzymes and non-enzymatic molecules. Venom- neurotoxins activate different reactions with nerve synapse – presynaptic and postsynaptic action; and induce anticholinesterase-induced flaccid paralysis. Myotoxins from Venom could induce systemic skeletal muscle damage. Hemotoxins induce the development of severe microcirculatory injury, damage to vascular membranes, thrombosis or bleeding. [6, 82, 84].

4.3 Radiation induced apoptosis and necrosis

Radiation induced Apoptosis and Necrosis as response of eukaryotic cells to influence of different types of radiation remain controversial. Radiation induced cell death by triggering apoptosis pathways was described in many articles and supported by many scientists [11, 15, 17, 39, 51, 52, 53, 54, 55, 56; 57, 58, 59, 62, 63, 74, 75, 76, 78]. However some scientists and some institutions described processes developing in irradiated eukaryotic cells as necrosis [24;34;38] and some scientists describing a variety of complex mechanism and mentioned that radiation-induced cell death could develop under different mechanisms of pathogenesis which include and apoptosis and necrosis. [1, 34, 38, 43, 77] Activation of

| Venom Toxins | Mechanism of Action | Symptoms |
|--|--|---|
| Polypeptide toxins. | Autonomic, Neurotoxic, Cardiotoxic, Myotoxic | Induce two forms of programmed cell death: cell apoptosis or cell necrosis. Presynaptic or postsynaptic actions. Induce excitation of some neurons. Neurotoxicity, Haemototoxicity. |
| Phospholipase toxins. | Presynaptic neurotoxic, myolytic, procoagulant, cardiotoxic, necrotic. | Induce cerebrovascular toxicity, cardiovascular toxicity. |
| Enzyme toxins: Transferases, Oxydoreductases, Hydrolases, Carbon-nitrogen lyases, Metalloproteinases. | Disorder of haemostasis, necrotic, haemolytic. | Blood vessel injury, blood cell lysis, brain tissue damage, heart muscle damage, liver damage, kidney damage. Neurotoxicity. Haemototoxicity. Skin damage. Hair follicle damage. |
| The Group of Toxins: Lectins, Nerve growth factors, Phospholipase inhibitors, Complement inhibitors, Proteinase inhibitors. | Cardiotoxic, Neurotoxic. | Anticoagulant proteins. Platelet aggregation inducers. Platelet aggregation inhibitors. |

Table 6. Venom toxins and mechanisms of action – biochemical and clinical classification.

cysteine proteases, cleavage of PARP - poly (ADP-ribosyl) ation of nuclear proteins causes the inner mitochondrial membrane to become permeable for ions and other small molecules during both types of cell death- apoptosis and necrosis. Many mechanisms of cell necrosis and apoptosis are identical – for example, degradation of the Nuclear matrix is a Common Element during Radiation-Induced Apoptosis and Necrosis [1,3,11,16,24,34,38,43,53,59,78].

Data from different sources described that the differences between apoptosis and necrosis are much less numerous than previously studies suggested. [1,78]. Joseph Dynlacht and his research group of scientists studied the outcome of human promyelocytic leukemia (HL60) cells irradiated with 10 or 50 Gy of X-rays and determined the mode of leukemic cell death. Different doses of X-rays induced different modes of cell death – cells irradiated with 10 Gy died by necrosis; cells irradiated with 50Gy died predominantly by apoptosis. [16].

The Cell Death Nomenclature Committee recommends the use of the appropriate diagnosis: apoptotic necrosis. [34]. Comparison and description of a cell's Necrosis and Apoptosis were provided by a group of scientists from different institutions and research groups [16,34]. Apoptosis is described as a normally active, programmed process of cell death devoid of inflammation and toxins. [16,34]. Necrosis possesses the characteristics of accidental or externally-induced cell death from the influence of different environmental factors and triggering development of inflammation and elaborating of toxins, release of pro-inflammatory active and toxic cellular contents into the intracellular and extracellular fluids and into the lymphatic systems and blood circulation [39,55,56,62]. Caspases are important molecular mechanisms and central components of the apoptosis process [39, 50, 51, 52, 54, 58, 62, 74, 75, 77, 78].

| Apoptosis | Necrosis |
|--|--|
| Inflammation never present. | Inflammation always present. |
| Toxic substances never present. | Toxic substances always present. |
| Morphologically cells shrinks, become denser, condensation occur, original name – shrinkage necrosis. Mitochondria's structure and functions are not affected. | Morphologically cells swelling, lysis. Mitochondria's structure and functions are affected. |
| Karyorhexis – pyknotic nuclear fragments. DNA broken into segments. | Karyolysis, Pyknosis, Karyorhexis. Nuclear swelling, Chromatin granular, Chromatin flocculation, Types of radiation induced damage of DNA: Breaks of the strand, alteration to bases, destruction of sugar, cross-links and formation of dimmers |
| Caspase activation always present. | Caspase depended initiation of developing of necrosis possible. Caspase-8 initiation possible with apoptosis and necrosis. |
| Genetic control initiate apoptosis | No genetic control, environmentally-induced |
| The Budding phenomenon. Cell membrane not affected | The Blebbing phenomenon, increased membrane's permeability. Cell membrane affected by external and internal factors. |

Table 7. Apoptosis and Necrosis: Comparison of Morphological and Biochemical features.

However, apoptosis is the principal mechanisms by which cells are physiologically eliminated. During apoptotic death, cellular dissociation by caspases of cell compartments occur and cell compartments and molecules are packaged into apoptotic bodies to avoid immune activation. [24,34,78]. Necrosis was considered in past times as passive, uncontrolled and unorganized mechanism of cell death. At the present time necrosis is considered as an alternative form of programmed cell death whose activation induces important biological consequences including immune reactions and induced inflammation. [43, 51, 52, 67, 74, 75, 77].

4.4 Inflammation induced by radiation

Radiation induces an important and aggressive inflammatory response in the irradiated tissues. [19, 20, 28, 30, 64, 65]. Acute Radiation Disease (ARD) or Acute Radiation Syndromes (ARS) were defined as a toxic, poisonous exposure with development of the acute pathological processes in irradiated animals: systemic inflammatory response syndrome (SIRS), toxic multiple organ injury (TMOI), toxic multiple organ dysfunction syndromes (TMOD), toxic multiple organ failure (TMOF) [2, 5, 18, 19, 21, 89, 90, 91]. Radiation-induced lung injury, radiation pneumonitis (RP), is a potentially fatal side-effect of thoracic radiation therapy [3, 4, 11, 15]. Radiation-induced thyroiditis: can occur after the use of radiation treatment and can result in lifelong hypothyroidism [18]. Irradiation of the liver with doses of 2,450-2,920 rads caused liver injury in 14 patients of 65 patients treated with radiation therapy [3, 28]. The clinical picture of radiation-induced hepatitis includes hepatomegaly, ascites, pleural effusion and alteration in liver function. Radiation injury of the central nervous system (CNS) has devastating and fatal clinical consequences and

severely limits the dose that can be delivered in the radiotherapy of brain, head and neck, pulmonary and other tumors [19, 28, 30, 64, 65]. Hematopoietic system toxicity is a major limiting factor in the use of aggressive, combined modality therapy (chemotherapy + radiotherapy) in the treatment of malignant disease [14, 22, 40].

Permanent anemia and pancytopenia can be caused by the reduced capability for cellular proliferation due to the stem cells injury produced by radiation. [14, 69, 70, 72, 76]. Radiation induces an inflammatory response in the irradiated organs characterized by leukocyte infiltration and vascular permeability changes and vascular injury [90, 99]. Vascular injury is a key determinant of acute and chronic organ intoxication and dysfunction associated with irradiation of the different systems, including the gastrointestinal tract [9, 19, 20, 22,]. Radiotherapy is used in the treatment of pediatric brain tumors and is often associated with inflammation and behavior changing following irradiation-induced inflammation and injury in the developing brain [19, 20]. The consequences of irradiation microglial loss can be secondary to injury from pronounced inflammation [19, 20]. A prominent inflammatory response occurs following both ischemic and hemorrhagic forms of microcirculation disorders [19, 20].

4.5 Roles of radiation toxins in developing of cellular structure radiation-induced injury

Radiation Toxins contained a group of biologically-active compounds which induce complicated but specific mechanisms of action with tissues and cellular damage. Radiation Toxins include a group of glycoproteins with high enzymatic activity against proteins, lipids, carbohydrates. Radiation Toxins contain a group of peptides with selective affinity to number of receptors and specific interactions with receptors of mammalian organisms. Toxins isolated from the irradiated mammals inhibit or activate a group of an ion channels, acetylcholine receptors, nicotinic receptors, membranes, coagulant/anticoagulant pathways. Our experiments involved injections to radiation-naïve animals of toxic doses of Radiation Toxins (SDR- group) which damaged endothelial cells of blood and lymphatic vessels, and injury to blood microcirculation in the brain, lungs, gastrointestinal tract, cardiovascular system. Administration (IV or IM) of the Haematopoietic Radiation Toxins to radiation-naïve animals induced development of anemia with reduction of hemoglobin concentration, reduction of red blood cell count and reduction of white cell blood count. Hematopoietic Radiation Toxins induced the development of hemolytic anaemia with accelerated destruction of mature red cells outside the bone marrow and destruction of pluripotent stem cells inside of the bone marrow. Radiation-induced hemolytic anemia occurred with intravascular and extravascular hemolysis. As a result of stem cell injury erythropenia, leukopenia, thrombocytopenia developed within days after irradiation. However, the acute hemolytic extravascular and intravascular anemia with lysis of erythrocytes, developed after high doses of radiation.

4.6 Development of radiation countermeasures

There are many sources of oxidative stress in the lives of workers, whether they work in nuclear power facilities, on the front lines of international conflicts, or in the reaches of outer space. The exposure dose can vary substantially, but at minimum will accelerate the aging of their organ systems, and at worse could result in acute exposure syndromes that may be fatal. A common thread of the oxidative stress exposures is ROS-binding to critical cellular

organelles and molecules, which can result in cellular dysfunction, mutation of nucleic acids, or even apoptotic cell death [107]. Currently there are no proven countermeasures for these exposures, aside from a clinical agent, Amifostine, (Etyhol™), which is used to reduce mucositis and other side effects from radiation therapy dose in cancer patients.

The cytotoxic effects of different types of radiation may be the single most important clinicopathologic process by which oxidative damage is induced from reactive oxygen species and radiation toxicity induced by radiation toxins. Radiation toxins (SRDs) with high enzymatic activity and their ability to degraded a wide variety of extracellular proteins, lipids, carbohydrates and DNA molecules, induce damage of important intracellular compartments such as mitochondria, ion channels, DNA, as well as activating degradation of peptide bonds in important polypeptides in tissues and vascular endothelium. Yet the exact mechanism by which radiation toxins stimulate development of the ARS is poorly understood.

Countermeasures against radiation toxicity can be developed both in oral formulas [109] and parenteral agents, e.g. Manganese SuperOxide Dismutase (MnSOD)-liposomes [108, 109] which can reduce radiation exposure-induced biological effects. The oral formulas consist of a combination of antioxidants and chemopreventive, anti-progression agents, which can reduce the likelihood of mild toxicity in acute low dose radiation exposures and tumor induction in chronic low dose exposures. The combination of oral formulas with higher dose reactive oxygen species scavengers, like Mn-SOD can improve survival in animals exposed to acute high dose total body irradiation [109]. In addition to these measures, active immunization by low, non-toxic doses of radiation toxins, (SRDs) can also be employed to reduce radiation toxicity. [104, 110] To be effective, SRD immunization must occur no less than 30 days before irradiation, and can be effective up to three years or more. Active immunization by radiation toxins can significantly improve the survival rate (up to 60%) versus placebo-controlled irradiated animals. Our studies attempt to show the potential ability of specific antibodies to neutralize radiation toxins and thus substantially reduce the effects on radiation-induced neuro-, vascular, gastrointestinal, and hematopoietic toxicity. [104, 110] Antiradiation antibodies prevent the radiation-induced cytolysis of selected groups of cells that are sensitive to radiation. Anti-radiation antibodies derived from different phases of the Acute Radiation Syndrome can compete with and thus prevent cytolysis mediated by cytotoxic lymphocytes. The therapeutic benefit of neutralization of SRD radiation toxins could make hemopoetic stem cell transplantation more effective. Antiradiation vaccine and IgG antibodies have shown activity in animals against several different types of radiation include gamma, heavy ions, and neutron irradiation.[104, 110]

Preliminary and pilot studies in vitro, in animal models and recently in humans, are showing some promise for both efficacy and safety/tolerability. [108-110] With current unpredictability in the operation of nuclear power facilities, potential radio-biologic terrorist weapons, and human operations in extreme environments, it is important to develop countermeasures to radiation toxicity in order to protect the potentially exposed. The first step in developing these countermeasures is to fully understanding the mechanism of toxicity, as is attempted to be summarized in this chapter.

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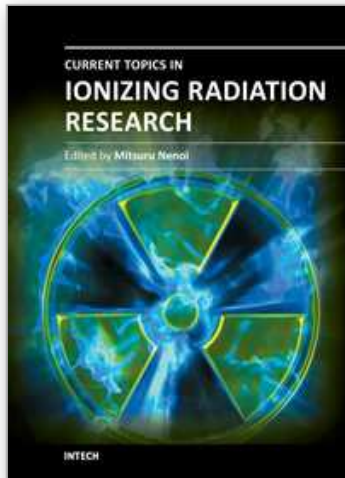
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Since the discovery of X rays by Roentgen in 1895, the ionizing radiation has been extensively utilized in a variety of medical and industrial applications. However people have shortly recognized its harmful aspects through inadvertent uses. Subsequently people experienced nuclear power plant accidents in Chernobyl and Fukushima, which taught us that the risk of ionizing radiation is closely and seriously involved in the modern society. In this circumstance, it becomes increasingly important that more scientists, engineers and students get familiar with ionizing radiation research regardless of the research field they are working. Based on this idea, the book "Current Topics in Ionizing Radiation Research" was designed to overview the recent achievements in ionizing radiation research including biological effects, medical uses and principles of radiation measurement.

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