

Performance Decrement by Exposure to Sub-Lethal Doses of Ionising Radiations

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ABSTRACT

Under many circumstances, exposure to ionising radiation can impede performance significantly. After large doses, lethal or supra-lethal, behavioural effects are rapid (within minutes), but up to 10 Gy, performance deficits develop rather slowly and are long-lasting. All tasks are not equally radiosensitive; tasks with complex and demanding requirements may be disrupted even at low radiation doses (<1 Gy). Combined injuries can act synergistically with radiation exposure to greatly increase behavioural deficits. Most of the radioprotectors developed to date are themselves behaviourally toxic at radioprotective as well as non-protective doses and the adverse effects are further aggravated in the presence of radiation. A very limited number of radioprotectors have been found to give behavioural radioprotection at very low, almost non-toxic doses.

1. INTRODUCTION

Behaviour is the basic manifestation of living organisms as they adjust to their physical and psychological environment. It is dependent upon a multitude of biochemical and electrophysiological functions at various morphological sites within the body, particularly within the nervous system and the brain. The nervous system's intimate role in behaviour makes it the presumed mediator of any environmental insult (including ionising radiation)-induced behavioural changes and performance deficits. Although the importance of the brain in radiation-induced behavioural changes is well established, it is not clear what specific changes in central nervous system (CNS) mediate the performance deficits after exposure to ionising radiation.

Contrary to the earlier belief that nervous system is relatively radio-resistant, of late it has been shown

that CNS is extremely sensitive to radiation, even at very low doses, in the range of 0.001-0.1 Gy¹. It is of particular interest that as early as in 1965, Mazumdar and Ray² observed potentiation of cerebral cortical activity (routine EEG) by very low doses of *in situ* radiation (1-2 millirads), while treating thyroid patients with oral radioiodine (¹³¹I). The authors stated that the radiation dose delivered to the brain was almost near background level and suggested further research in this direction.

Radiation has significant effects on a variety of behavioural expressions, including learning, memory, performance and social and consumption behaviour. Post-irradiation changes in behaviour may reflect deficits in either performance or learning or both. Performance may be separated into tasks having a strong cognitive component or a strong motor component.

2. EFFECTS OF RADIATION ON DIFFERENT FUNCTIONS

2.1 Functional Sensitivity of Brain

Different regions of the brain may have varying susceptibility to ionising radiations. Functional radiosensitivity of specific brain regions (nuclei) may partly explain the ability of a particular dose of ionising radiation to disrupt one type of behaviour but not another one. For example, monkeys continue to perform a visual discrimination task but not a more physically demanding task after a similar dose of ionising radiation (20 Gy)³. It has been assumed that classically conditioned reflexes are more radio-resistant than motor coordination.

Cortical EEG changes were observed in humans and animals receiving doses⁴ of < 0.05 Gy. Post-irradiation spike discharges are observed more in hippocampal EEG than in cortical⁵ EEG. Hippocampus has been long recognised as being exceptionally vulnerable to numerous insults⁶. The apparent radiosensitivity of hippocampus and its importance in critical functions like learning, memory and motor performance have triggered further investigations on the electrophysiology of this brain region. The firing of hippocampal neurons has been observed to be altered by exposure to 4 Gy gamma radiation⁷. *In vitro* experiments showed that spontaneous discharges of hippocampal pacemaker like neurons are induced by X and gamma-rays at a dose⁸ of 0.008 Gy. It has been observed that years after clinical irradiation dysfunction of the hypothalamus is prominent without evidence of hypothalamic necrosis⁹. Various mechanisms have been suggested as causative factors for radiosensitivity, such as sparse microvasculature or aspects of highly sensitive hippocampal electrophysiology. Further work with hippocampal slices from guineapigs has revealed that hippocampal neuronal physiology could be significantly altered by free radicals¹⁰. It is known that ionising radiations generate highly reactive oxygen free radicals leading to lipid preoxidation of cell membrane, impaired synaptic efficacy, calcium influx into the cell and cell death. Lipid preoxidation is inversely related to dose rate¹¹, and low level of free radicals inhibits maintenance of long term potentiation¹² (LTP), related to learning and memory processes. Taken together, it seems that alteration

of hippocampal function may lead to behavioural changes and performance decrements under certain conditions, such as exposure to ionising radiation.

2.2 Learning & Memory

Studies have suggested that learning can be altered by exposure to radiation even at low levels (< 0.1Gy). Rats were trained to stay in lighted area to avoid foot shock in the adjacent dark area. A rapid movement into the hazardous chamber suggested deficit in learning. This kind of learning appears to be extremely sensitive to radiation exposure. Exposure to electrons in the dose range 0.001-0.1 Gy can produce retrograde amnesia, an inability to recall recent events following trauma or a novel event (radiation). The duration of amnesia lasts for a few seconds and is dependent on dose rate (electron or gamma radiation). The mechanism of radiogenic amnesia is not known¹.

Improved or unaltered learning capacity or performance after exposure to radiation has been reported. Though radiation caused dose-dependent decrease in activity (body movement) and appetite, monkeys showed no loss of ability to solve problems at doses of 2-10 Gy X-radiation¹³. Task performance was enhanced in some studies¹⁴ after 6.5-10 Gy X-rays. It has been suggested that radiation could act as a mild sedative, thus reducing anxiety, tension and distraction¹⁵. Though some of the behavioural radiobiology reports in literature suggest that learning and performance are radio-resistant, most studies have reported post-irradiation deficits¹⁶.

2.3 Cognitive Performance Tasks

Tasks in this category require discrete physical movements and functional cognitive processes, such as timing, decision-making or concept formation. Experiments with monkeys have led to important results, which will have relevance to the performance of pilots after a nuclear confrontation, in order to assess crew and aircraft vulnerability and survivability. They involved 10 Gy or less doses of either neutron or gamma radiation delivered in dose rates simulating either combat (rapid doses) or fallout (protracted doses). In a fallout study (a dose of 3 Gy delivered over 12 hr) monkeys performed a discrete response

task (operant behaviour), which required pressing a lever after a light comes on either for food reward or shock avoidance. A loss of efficiency occurred in two of eight negatively-reinforced monkeys and in two of seven food-reinforced monkeys. Delayed reaction time was noted in three monkeys of each group. In addition, four food-reinforced monkeys and one avoidance monkey showed emesis (vomiting)^{17,18}. Apparently, >50 per cent of this population was affected behaviourally, resulting in performance decrement.

In another pilot simulation study, monkeys were required to maintain their chairs in an upright position by compensating for pitch and roll to avoid shock. Ionising gamma radiation (3 Gy) was delivered over 72 hr at dose rates of 0.014 Gy/min to 0.01 Gy/hr. Performance was relatively unimpaired, but all subjects demonstrated classic prodromal symptoms (nausea-vomiting)^{19,20}. Other simulation studies revealed that as post-irradiation time increased, the performance of the subjects worsened gradually²¹. These studies indicated that either emesis alone or similar direct behavioural effects may be sufficient to prevent pilots from flying military missions.

2.4 Early Transient Incapacitation and Early Performance Decrement

For military, an abrupt inability to perform, viz. early transient incapacitation (ETI), is a potentially devastating behavioural consequence of radiation exposure. A less severe variant of ETI is early performance decrement (EPD) in which performance is significantly degraded rather than totally suppressed. Until recently, it was presumed that ETI and EPD would occur only at supra-lethal doses, but more recent data have revealed that EPD may occur at lower doses in various animal species, including humans²². The radiation dose required to disrupt behaviour is directly related to the complexity and demanding nature of the task. Regarding performance task of monkeys, it has been observed that disruptive dose of ionising radiation might be very low (sub-lethal) when the task is difficult, requiring both visual discrimination and memory. It has been presumed that this might be true in humans, when relatively low doses may cause rapid transient disruption in performance²³.

3. DOSE, DOSE-RATE AND QUALITY OF RADIATION

Ionising radiation can sometimes produce behavioural changes²⁴. In monkey and rat experiments, at lethal dose, the incidence of performance^{4,22,25} suppression was observed to range from 10 per cent to 90 per cent. Dose-rate can also influence behaviour. Monkeys trained to perform a delayed matching to sample task involving visual discrimination and short-term memory were exposed to 10 Gy gamma radiation at dose rates of 0.3-1.8 Gy/min. Only 7 per cent of the subjects demonstrated transient EPD at a dose rate of 0.3 Gy/min, while 81 per cent showed behavioural decrement at 1.8 Gy/min dose²³. In addition to dose and dose rate, the type of radiation also can influence early behaviour deficits. It is generally accepted that high linear energy transfer (LET) radiations (such as neutrons) are more effective in eliciting biological responses and death than low LET radiations (such as gamma rays)²⁶. However, research has shown that electron radiation was most effective in producing EPD and neutron radiation was least effective. Gamma radiation was slightly more effective than neutrons^{25,27,28}.

4. COMBINED INJURIES

In nuclear confrontation apart from radiation injury, the victims might experience burns, wounds, trauma from chemical agents and environmental stresses, such as desert climate, cold and hypoxia in the mountains. Behavioural consequences from combined injury and trauma from irradiation are less known. It is assumed that environmental and combat stresses may also combine with radiation injuries to increase behavioural decrements. A study in monkeys indicated synergy between radiation and motion, revealing an emesis ED 50 of 4.5 Gy for radiation alone and 2.6 Gy for radiation plus motion²⁹⁻³². In a study on the combined effects of radiation and an anticholinesterase agent (physostigmine), rats were evaluated for behavioural changes. After 45 minutes post-irradiation, the radiation-only group had a 30 per cent deficit in performance, the physostigmine-only group had a 40 per cent deficit, while the combined treatment group showed a performance³³ deficit of 60 per cent.

Other environmental stresses can alter the effects of radiation on behaviour or lethality. For example, daily exhaustive exercise, continuous exposure to cold, or continuous exposure to high altitude considerably reduced the resistance to radiation-induced changes and mortality³⁴. It has been suggested that behavioural effects of radiation may summate or act synergistically with other stresses.

5. DEFENCE IMPLICATIONS

During nuclear emergencies, it has been assumed that the targeted battle force would receive an initial radiation dose of 1.5-30 Gy, with weapon strength³⁵ of 50 kt or less in the first one minute. But apart from the instant lethal dose, army personnel and civilians, away from the epicentre, would be exposed to sublethal doses of radiation, either in normal work or rescue operations. A major concern of the military planners is whether military personnel will be able to perform their duties after exposure to radiation. The degree to which irradiation affects operations may depend on the nature of duties and the consequences of non-performance. The more critical the role of one or a few individuals in successfully completing a mission, the more important is the issue of non-performance. For example, a jet fighter pilot might tolerate less of a performance decrement than an infantryman. In fact, modern war is extremely sophisticated, using complicated weaponry systems, where minimal in-attention or lack of alertness of the combat forces, due either to direct effect of radiation or to emetic effect of radiation, might be highly disastrous.

From known human experiences with radiation (accidental), it has been observed that supra-lethal doses produced ETI and EPD invariably, followed by confusion, irritability, restlessness, coma and death³⁶. In comparison to high dose accidents, lower radiation doses may produce mild but persistent behavioural changes characterised by weakness and fatigability³⁷. Latent period of onset of nausea and vomiting seems to be inversely related to radiation dose³⁸. The Chernobyl nuclear reactor accident also produced behavioural deficits in persons attempting to perform their duties in high radiation environment³⁹. These recent data suggest that sub-lethal doses of radiation can induce human performance decrements.

5.1 Evaluation & Underlying Mechanisms of Action

To develop strategies for prevention of performance deficit in response to ionising radiation, a Behavioural Radiobiology Laboratory has been established at the Institute of Nuclear Medicine & Allied Sciences (INMAS), Delhi. Initially, a few experimental systems have been designed and fabricated at the Institute workshop and methods have been standardised for assaying radiation-induced alteration in behaviour and the subsequent preventive measures to be undertaken. Behavioural expressions are multifaceted and evaluation requires a number of parameters to be tested to obtain a unified viewpoint. For example: (i) radial arm maze, for assessment of orientation problem and spatial memory; (ii) multiple-T-maze for learning; (iii) anxiety stand for additional stress of anxiety in relation to radiation; (iv) rota rod for

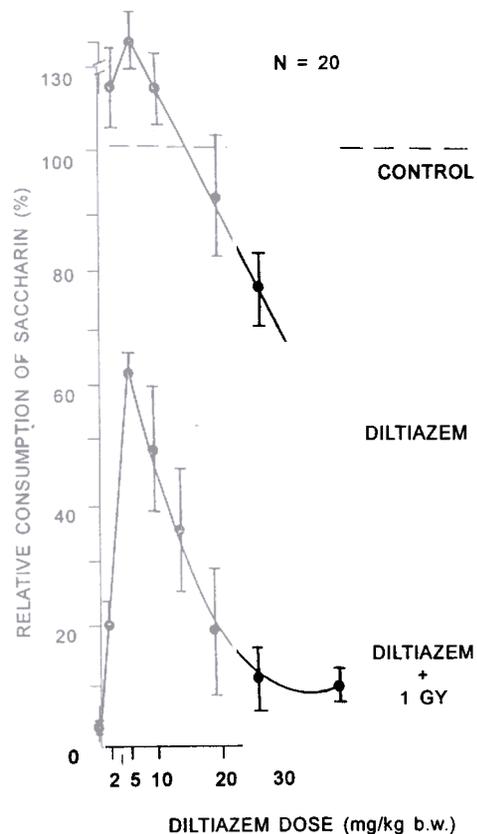


Figure 1. Effects of various doses of diltiazem (administered i.p. 20-30 min prior to radiation exposure on CTA response in 1 Gy whole body gamma irradiated rats⁴¹ (n = 20).

strenuous activity; and (v) conditioned taste aversion (CTA) for evaluation of radiation-induced nausea and vomiting. More complex equipment, such as discrimination chamber and operant behaviour techniques are also used for specific behavioural expressions. Initially, two modalities were utilised for behavioural radioprotection work: (a) CTA in rats in response to radiation, and (b) radial arm maze, for studying spatial memory and learning in mice.

CTA method is very sensitive and reliable and can occur at doses⁴⁰ as low as 0.25 Gy. Diltiazem has been evaluated through CTA in rats and for spatial memory in mice. It has been observed that diltiazem at radioprotective and substantially at lower doses (>10 mg/kg b.w. i.p.) evoked CTA alone in a dose-dependent manner and the degradative effect⁴¹ was further aggravated in the presence of radiation (Fig.1). But diltiazem at a lower dose (<10 mg/kg b.w. i.p.) offered significant protection to radiation-induced CTA (62 ± 2.5 per cent) (Table1). In spatial memory test with mice diltiazem alone and also in the presence of radiation degraded the performance but at a lower dose (<10 mg/kg b.w.), it improved the performance⁴² significantly (Fig.2). Interestingly, when diltiazem was administered orally (~10 mg/kg b.w.) for 10 days and discontinued for

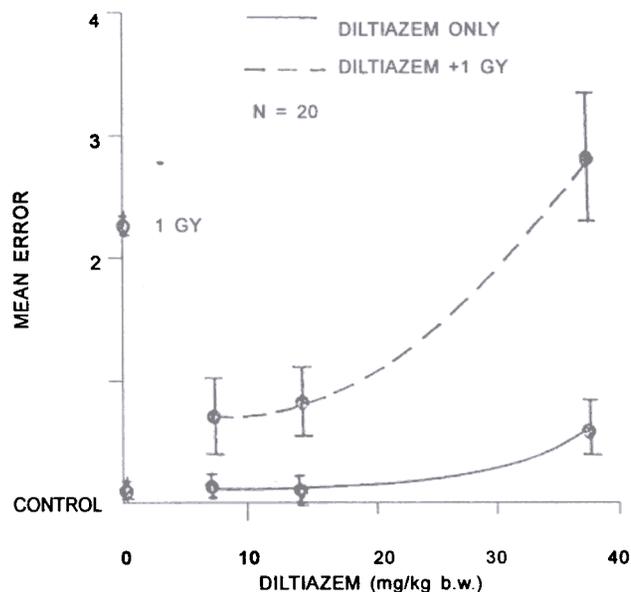


Figure 2. Effect of various doses of diltiazem (injected i.p. 20-30 min prior to 1 Gy whole body gamma irradiation exposure) on performance of mice in radial arm maze. Mean error is expressed in terms of revisits to the arms⁴¹ (n=20).

24 hr prior to irradiation (1Gy), it rendered 50±5 per cent protection to CTA in rats. This finding is of particular interest for future development of a potent oral behavioural radioprotectant, because (a) metabolism of diltiazem in the body is very fast (drug half-life 4-6 hr in humans and 2-3 hr in rodents), (b) 5-10 mg/kg b.w. diltiazem represents 40-80 mg/70 kg individual human, or almost therapeutic⁴³⁻⁴⁴ dose (30-90 mg / 70 kg, 6 hourly or 120-360 mg per day). In a different series of experiments, hoeschst, radioprotector and *panax ginseng* have been evaluated singly or in combination against radiation-induced CTA in rats. Hoeschst (2 mg/kg b.w. i.p.) gave remarkable protection against radiation-induced CTA. Prior administration of *ginseng* also offered excellent protection against CTA (94.3± 4.7 per cent in the presence of radiation, and in combination with diltiazem at a low dose (5 mg/kg b.w.), CTA protection was enhanced synergistically (123 ± 3.3 per cent). Apart from *ginseng*, ondansetron, the effective anti-emetic in humans, was also evaluated for mitigating radiation-induced CTA in rats and was found moderately effective against 1 Gy gamma whole body irradiation (Table 1). The latter observations indicate that suitable combinations of non-toxic substances could prevent radiation-induced behavioural

Table1. Effects of radiomodifiers on gamma ray (1 Gy)-induced CTA in rats

Radiomodifier	Δt (min)	Relative saccharin consumption (% of control)	
		D = 0 Gy	D = 1 Gy
None (control)	-	100	3.0±1.0
Diltiazem (5mg/kg b.w.)	-20	132±4.0	62.0±2.5
Ondansetron (2mg/kg b.w.)	-120	125±2.2	42.0±1.9
Hoeschst (2 mg/kg b.w.)	-120	98±5.6	72±5.4
Ginseng (50 mg/kg b.w.)	-30	101±2.9	94.3±4.7

CTA is expressed in terms of percentage consumption of saccharin solution in comparison to pre-exposure control values. (<14.5+2ml) Diltiazem, Ondansetron, hoeschst and *ginseng* were injected intraperitoneally prior to whole body gamma irradiation, Δt is the time interval between administration of the radiomodifier and irradiation.

in monkeys, apparently without performance decrements⁴⁶

Serotonin plays a vital role in X-irradiation-induced emesis⁴⁷, which is similar to that caused by chemotherapeutic agents employed for tumour chemotherapy⁴⁸. Selective antagonists of serotonin S_3 receptors (e.g. ondansetron) prevented emesis induced by chemotherapeutic agents like cisplatin in laboratory animals^{49, 50}. Ondansetron as well as granisetron (S_3 receptors antagonist) had high efficacy against nausea and vomiting induced by chemotherapeutic agents and irradiation⁵¹ and is well accepted in clinical practice. Recently, both ondansetron and granisetron were evaluated separately for psychomotor and cognitive performance in human volunteers and were found to be extremely well tolerated with no obvious side effects⁵². The only disconcerting findings are occasional headache (20 per cent), less effective against nausea than vomiting and delayed nausea-vomiting⁵³.

Radiation-induced CTA in rats is equivalent to nausea-vomiting (emesis) in humans. There are many similarities between emesis and CTA and the neural response pathways of emesis and pica in rats (eating of non-nutritive substances, such as kaolin), an illness-response behaviour⁵⁴. Gastric mucosa contains large stores (~90 per cent of total body content) of serotonin⁵⁵. Radiation-derived free radicals somehow trigger serotonin release system from intracellular storage sites⁴⁷. Subsequently, serotonin interacts with S_3 receptors present on visceral afferent nerve endings and sends impulses to the chemoreceptor trigger zone (CTZ), which transmits information to the vomiting centre, leading to vomiting motor reflex, pica or CTA.

5.3 Learned Task Performance

Two types of equipment have been designed and developed for study of task performance: (a) radial arm maze (mice)—for studying spatial memory and short and long-term memory. The apparatus consists of eight identical arms radiating from a central arena. All the arms are baited and the animal starved overnight, one at a time is placed in the central platform and is allowed to consume all the food in a specific time and in a specific

movement pattern (clockwise or anticlockwise). In a few days, the animal learns the task without error (re-entry to the arm); then the animal is exposed to 1 Gy whole body gamma irradiation. Post-irradiation movement of the animal becomes haphazard, accompanied by mistakes. Prior administration of diltiazem at a low dose (<10 mg/kg b.w.) prevents behavioural abnormality; (b) Multiple-T-maze consists of a number of T-shaped alleys fused together to form a long path punctuated with mistake points and one way swing-doors. At one end, a food chamber is provided and at a farther end is the entry point. The overnight-starved animal one at a time is placed at the entry point and is allowed to search the food chamber. In a short time, the animal learns to reach the food chamber. After irradiation (1 Gy), the running time is observed to get shortened, indicating radiation-induced enhancement of activity; the latter finding corroborates the earlier finding³⁴.

5.4 Behavioural Radioprotection

Relatively few studies have addressed the problem of normalising behavioural changes immediately (and up to 24 hr) after irradiation. Traditionally, chemical radioprotectants were meant to protect against the lethal effects of ionising radiation⁵⁶. Recently, radioprotective compounds have been evaluated for their ability not only to decrease mortality but also to preserve behavioural integrity after irradiation^{57,58}. A radioprotective drug or regime should be able to provide sufficient protection, well tolerated, compatible with a wide range of compounds, with no cumulative or irreversible toxicity, capable of being self-administered and must not interfere with performance. Unfortunately, till recently, although many radioprotectants have been developed (aminothiols or aminothiol derivatives), and many of them offered significant protection against radiation-induced lethality, all are behaviourally toxic. WR-2721 (ethiofos), a phosphorothioate, developed by the US Army, an excellent radioprotectant, has been extensively evaluated for its side effects and found to be behaviourally toxic⁵⁸. In all the species tested, (mice, rats, and monkeys), ethiofos disrupted behaviour and performance when administered alone, and in the presence of radiation degradation was further aggravated⁵⁹⁻⁶¹.

In the search for a chemical radioprotector which might be least toxic, a novel approach had been initiated by testing thiol compounds not designated for radioprotective activity, but known for their use in other contexts with favourable therapeutic index. This included diltiazem, a benzothiazepine and calcium channel blocker, used for cardiovascular patients. It was observed that diltiazem offered significant protection (93 per cent) against lethal whole body gamma irradiation in mice⁶². A calcium antagonist might attenuate radiation-induced injury by inhibiting cellular calcium overload subsequent to cell membrane damage by radiation-generated free radicals. In view of their good tolerance, calcium antagonists may be applied safely in situations of radiation exposure, including radiotherapy and internal radionuclide contamination.

From military standpoint, radioprotectors will have their greatest utility during nuclear emergencies, when their use would protect personnel and maintain performance capability of the combat forces. Most of the effective radioprotectors developed to date exhibited adverse reactions and performance decrements. Literature shows that it may be possible to use combinations of agents with different radioprotective mechanisms of action at less toxic doses⁶³. Coordinated action between the agents might promote protection efficacy at the required level without behavioural toxicity. Moreover, natural substances could be evaluated for radiation protection. A number of herbal products, which are non-toxic in nature, are being used by humans for various health purposes. Recently, *tulsi* (*Ocimum Sanctum*) has been found to give protection against lethal (11 Gy) radiation in mice⁶⁴. The authors claimed that the radioprotective dose is far below the toxic (LD_{50}) dose. The author's findings with diltiazem at low doses (comparable to human therapeutic doses) as behavioural radioprotectant are very promising for future development of behaviourally non-toxic radioprotectants.

6. CLINICAL IMPLICATIONS

Radiation therapy has become an effective treatment modality for some forms of human brain cancers, but the total tumoricidal dose is limited by the radiotoxicity to normal tissues. Because of this

limiting factor, the response of normal tissue to radiation has been of considerable interest and concern.

Radiation injury to the brain with conventional daily dose of 1.8 Gy to 2 Gy given five times per week, total doses of 60-80 Gy is without any significant acute effects. Daily dose fractions larger than 6 Gy may lead to severe complications. The major risk of high dose irradiation of brain is late delayed injury. Recently there has been considerable interest in use of implanted radionuclide sources for the treatment of brain neoplasms (brachithrapy), but focal irradiation injury poses the most serious problem. It has been also observed that during cranial radiation therapy there is substantial risk of intellectual deterioration in patients leading to significant alterations in their quality of life⁶⁵.

6.1 Radiation Sickness

Irradiation in absence of flash, detonation and thermal pulse, occurs without any sensation. Even after a dose of several hundred centigrays (cGy), exposed individuals may remain perfectly normal and asymptomatic for 1-2 hr after irradiation⁶⁶. The various tissues of the body have different degrees of sensitivity to radiation injury. The most sensitive is bone marrow, followed by gastro-intestinal tract, the cardio-vascular system and finally the central nervous system (CNS). Exposure to a sufficient amount of radiation causes radiation sickness in man, which is manifest in characteristic clinical sequelae, known as acute radiation syndrome (ARS). The manifest illness of the ARS is divided into three major forms: haemopoietic, gastro-intestinal and central nervous system syndrome. The haemopoietic and gastro-intestinal syndromes are considered the major mechanisms of death for doses less than 20 Gy, whereas death occurs due to CNS syndrome with neuro-vascular complications at doses above 20 Gy. The haemopoietic syndrome is anticipated when radiation dose greater than 1Gy is received. In most cases, the syndrome is uncomplicated by the effects of gastro-intestinal damage until the dose received is between 8-10 Gy. Above 10 Gy, death follows 4-5 days post-irradiation.

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