REVIEW

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REVIEW

Responding to radiation accidents: what more do we need to know?

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Abstract

A short review of the various types of radiation incidents and accidents that have occurred is used to provide a context for discussing the findings on medical management of the victims of such incidents and accidents reported in a recent Special Issue of the Journal of Radiological Protection. The review demonstrates that accidents and incidents giving rise to high radiation doses may involve over-exposure of a single individual, a few individuals, or very large numbers. In general, these exposures will be relatively short-term, ranging from a few seconds to a few days, but chronic situations resulting in high exposures can occur. Some of these exposures may be highly localised, whereas others may result in almost uniform whole-body irradiation. This diversity of situations means that it is not feasible to have a single protocol for the diagnosis and treatment of over-exposed individuals. If the over-exposures are limited to one or a few individuals, these can be addressed on a case-by-case basis. However, where large numbers have been exposed or may have been exposed, there is a need to implement a rapid and effective system of triage. Furthermore, this system is likely to have to be implemented by individuals who have little or no direct experience of radiation-induced injuries. For those individuals who may have been significantly exposed, the key consideration is not to determine the radiation dose that they have received, but to establish their present clinical status and how it is likely to develop with time. There is at most a very limited role for bone-marrow transplantation in the treatment of acute radiation syndrome, whereas there are good arguments for administering various treatments to boost bone marrow function together with other supportive interventions, e.g. in control of infections and handling both fluid loss and bleeding. However, there is concern that the focus to date has been only on the licencing of drugs related to the management of haematopoietic effects. Although a great deal is known about the diagnosis and treatment of injuries arising from high dose exposures, this knowledge is biased towards situations in which there is relatively uniform, external whole-body exposure. More attention needs to be given to assessing the implications of various inhomogeneous exposure regimes and to developing medical countermeasures optimised for addressing the complex, multi-organ effects likely to arise from such inhomogeneous exposures.

1. Introduction

Although major accidents, such as those at Chernobyl and Fukushima, tend to be the focus of media and public attention, it is important to recognise that smaller-scale accidents and incidents involving radioactive materials have the potential to give rise to significant radiation exposures to, and early adverse health effects on, small numbers of individuals (typically ranging from exposure of a single individual to up to several tens of individuals). These accidents and incidents have arisen in the context of industrial uses of sealed radioactive sources, notably in industrial radiography, uses of sealed and unsealed radioactive sources in diagnostic radiology, nuclear medicine and radiotherapy, criticality accidents and other miscellaneous types of incidents and accidents. Overall, more than a decade ago Nénot (2009) estimated that since the end of World War II there had been at least 600 events that caused significant radiation exposures of about 6000

individuals, with about 70 accidents resulting in one or more fatalities each. In total, there were about 200 deaths due to acute radiation syndrome. Since the review by Nénot (2009) many more accidents have occurred (Holmberg and Pinak 2021). A comprehensive review of all types of incidents and accidents covering the period 1980–2013 is provided by Coeytaux *et al* (2015). The historical and ongoing occurrence of such events sets the scene for the continuing need to address the medical management of radiation incidents and accidents.

Herein, a short review of the various types of incidents and accidents that have occurred is provided (section 2). This gives an indication of the ranges of doses received, the periods over which those doses were delivered, the degree of inhomogeneity of exposure, and the effects observed. It does not aim to be comprehensive and differs from the review by Holmberg and Pinak (2021) because the latter focuses mainly on incidents and accidents that have occurred in the context of medical diagnosis and treatment. The review in section 2, complemented by the information in Holmberg and Pinak (2021) provides a context for a discussion of approaches to the medical management of high radiation doses that is based largely on the papers included in this Special Issue of the Journal of Radiological Protection, co-ordinated and introduced by Valentin and Stenke (2022). This discussion is included in section 3. Based on the information on historical incidents and accidents and the most recent information on medical management included in this Special Issue, section 4 draws some conclusions concerning areas where additional knowledge would be desirable, and points to the broad areas of research that would be involved in acquiring that knowledge.

Overall, the material included in the Special Issue and reviewed in section 3 indicates that although a great deal is known about the diagnosis and treatment of injuries arising from high dose exposures, this knowledge is biased towards situations in which there is relatively uniform, external whole-body exposure. As discussed in section 4, more attention needs to be given to assessing the implications of various inhomogeneous exposure regimes.

2. Incidents and accidents that have occurred

2.1. Industrial radiography

The International Atomic Energy Agency (IAEA) (1998a) compiled details of a substantial number of accidents and incidents that had occurred in industrial radiography, with a view to identifying the principal and contributing causes of such accidents and incidents. This compilation illustrates that many such incidents involve an equipment failure compounded by an inappropriate response often due to a lack of training, experience and/or supervision. In some cases, a lack of appreciation of safety issues and a poorly developed safety culture were primary issues leading, for example, to individuals deliberately defeating safety interlocks or other safety systems, or going beyond their competence, e.g. in attempting source-recovery actions. Subsequent accidents of this type are described in more recent IAEA reports (IAEA 2004a, 2009).

The radiological consequences of the various incidents differed enormously depending upon whether exposure arose from an x-ray unit or a source, the activity of the source, and the duration and other aspects of the exposure situation. In some cases, the doses received were as small as a few millisieverts, whereas whole-body doses of more than 1 Sv were received in some accidents, leading to the induction of acute radiation effects in some exposed individuals and leukaemia in others. Acute effects were typically skin burns, either of the extremities or of the chest where source assemblies had been placed in shirt pockets.

2.2. Radiotherapy and nuclear medicine

Some types of incidents that can arise in radiotherapy are described below. These incidents illustrate that errors in equipment calibration or operation are of particular concern, because they have the potential to adversely impact substantial numbers of patients treated sequentially using the incorrectly calibrated or malfunctioning equipment. It is emphasised that these are examples only and that numerous other examples could have been selected.

A detailed report on the accidental overexposure of radiotherapy patients in San José, Costa Rica has been published by the IAEA (1998b) and a summary has been provided by Nénot (2009). Errors in the calibration of a new Co-60 radiotherapy source resulted in 114 patients receiving exposures that were 50%–60% higher than prescribed. The error resulted from a confusion in the time units adopted between the second and 1/100th of a minute. The error was recognised only after about one month when a large series of patients exhibited abnormal signs of radiation injuries. The over-exposures resulted in severe consequences, sometimes worsened by sub-optimal treatment procedures. Severe effects in four patients included quadriplegia, paraplegia, spinal-cord demyelination, and severe digestive and cutaneous injuries. Marked effects occurred in a further 16 patients. Nénot (2009) estimates that among 61 deaths within two years of the accident, 13 could be directly attributed to their over-exposures and four to radiation-induced

complications. In addition, among the 51 patients still alive two years later, two were suffering from late severe complications and 12 exhibited marked and disabling effects.

In an earlier incident in Columbus, Ohio between 1974 and 1976, an incorrect calibration of a Co-60 source led to 426 patients receiving doses that were 15%–45% higher than prescribed. Among the 183 patients still alive one year after treatment, more than one third had severe complications of the central nervous and gastrointestinal systems. Conversely, in Stoke-on-Trent, UK between 1982 and 1991, 1045 patients received doses 5%–35% lower than expected, but the consequences of these under-exposures are difficult to evaluate, though they are likely to have compromised the efficiency of treatment. It is possible that incidents involving under exposure are not as fully reported as incidents involving over exposure. Also, under exposures, if recognised soon after treatment, may potentially be compensated by altering the treatment regime. Various other accidents have occurred in hospital contexts, e.g. arising from errors in programming, from disposal of a catheter containing an Ir-192 brachytherapy source, from adaptation of a computerised treatment to incorporate additional shielding and from malfunctioning of a linear accelerator used for the treatment of breast cancer (Nénot 2009). This malfunctioning resulted from a transitory loss of electrical power that caused an automatic shutdown of the accelerator. Following the restoration of electrical power, the machine was restarted after its controls had been checked. However, subsequent dosimetry measurements revealed that the output of the accelerator was significantly higher than expected. Further checks revealed that the dose monitoring system was not functioning properly, and that one of the electronic components of the safety interlock system was damaged. Thus, the over-exposures resulted from faults developed in two separate electronic circuits (IAEA 2004b).

2.3. Criticality

Criticality accidents were relatively common in the first two decades after World War II, but only six process-related accidents have been reported since 1966. In total, 22 accidents are known to have occurred in process facilities, whereas 38 are known to have occurred during critical experiments or in operations with research reactors. Details of all 60 accidents are presented in McLaughlin *et al* (2000). The characteristics of process accidents are different from those arising in critical experiments or in work with research reactors. Process facilities aim to avoid criticality accidents through physical and administrative controls. Nevertheless, in process facilities and under normal working conditions, operatives, who are not generally specialists in criticality, can be close to potentially critical configurations. Therefore, if physical and/or administrative controls fail and a criticality accident occurs, large acute radiation doses may be received by persons local to the accident. In contrast, research reactors and experimental configurations studying issues related to criticality are usually staffed by operating personnel with expertise in criticality physics. Furthermore, although the staff carry out hands-on work with fissile materials, operations in which critical or near-critical configurations are planned to arise are generally undertaken remotely. Thus, in the event of criticality accidents the staff will often incur only small radiation doses.

When a criticality accident occurs, the primary consequence is the release of one or more pulses of neutrons. Multiple pulses may occur, for example, if the first pulse changes the geometry of the system decreasing its reactivity but the geometry changes back after the pulse with an increase in reactivity. For example, in an aqueous system the heat generated by the first pulse of neutrons may evaporate some of the liquid present, decreasing the moderation and hence the reactivity of the system. However, if further liquid then enters the system, the reactivity will increase, and a second pulse of neutrons may be generated. The generation of a second pulse is illustrated by an accident at the Oak Ridge Y-12 plant in 1958 (Process Accident 4 in McLaughlin *et al* 2000). In this accident, uranyl nitrate solution was drained from small-diameter vessels into a 55-gallon drum, which is a compact geometry that is more conducive to criticality. After about 15 min, an initial criticality arose, contributing about 6×10^{16} fissions. It is thought that this first pulse generated enough radiolytic gas bubbles in the solution to reduce the reactivity. However, about 15 s later, when these bubbles had left the system, a second and larger pulse occurred. Subsequent smaller pulses occurred over the next 2.6 min, until the system started to boil, which reduced its reactivity. The total number of fissions in this accident was about 1.3×10^{18}, i.e. a factor of 20 larger than in the first pulse.

McLaughlin *et al* (2000) summarise the main characteristics of the 22 process accidents that have occurred. Adverse health effects were mainly incurred by process operatives and included nine fatalities plus three survivors who required limb amputations. In contrast, only one accident resulted in measurable fission-product contamination and only one resulted in measurable (but small) doses to members of the public.

Reactor and critical experiment accidents have been much more diverse than process accidents, though with total fission yields spanning much the same range. A total of 12 fatalities have occurred in accidents involving bare and reflected metal systems and in moderated metal and oxide systems. These fatalities

typically occurred when near-critical assemblies were being constructed or modified by hand by individuals with expertise in criticality. They typically reflected errors of judgement by the operatives often combined with violations of operating procedures. In addition, in one accident at a research reactor, saturation of neutron-detection instruments led to misinterpretation of the state of the reactor.

2.4. Other incidents and accidents

A wide variety of other incidents and accidents have also occurred. Such accidents often involve exposure of a significant number of individuals and/or relatively extensive contamination of the environment. Because of their significance, each such accident is usually the subject of a report published by the International Atomic Energy Agency (IAEA) and developed in conjunction with other relevant agencies that reviews both the characteristics of the accident and the response to it. Here, information on some of these various accidents is collated in summary form to illustrate the various contexts in which they may occur.

2.4.1. Loss or abandonment of radiotherapy sources

Radiotherapy sources typically contain large amounts of gamma-emitting radionuclides and are susceptible to being lost, abandoned or stolen. These sources may subsequently be disassembled. Thus, in Juarez, Mexico in 1983 a teletherapy machine containing 15.6 TBq of Co-60 in 6000 pellets was dismantled. During disassembly, 800–1000 pellets were spilt into a truck bed and recycled via a scrap yard and iron foundries. Consequently, about 4000 members of the public were exposed to non-trivial doses, with 800 receiving more than 50 mSv and eight between 1 and 7 Gy. Because of the protracted nature of the exposures no deaths occurred. However, rehabilitation of the environment took four months and necessitated control of 17 000 houses of which 800 were destroyed because they were judged impossible to decontaminate (Nénot 2009).

In 1987, in Goiânia, Brazil, a similar accident resulted in much more severe consequences because the 51 TBq source was made of highly soluble Cs-137 chloride. Early symptoms of acute radiation syndrome in two scrap dealers were attributed to tropical disease, before the radiological nature of the incident was suspected by an oil prospector. Because of the wide distribution of the radioactive material large numbers of people had to be monitored for contamination. In total, four victims died and 28 had to undergo surgery, comprising grafts or amputations. Internal doses were of significance, particularly amongst children who had played with the 'magic' luminescent powder. Large quantities of radioactive waste were generated, and it took ten years to find a viable solution for dealing with this material (IAEA 1988, Nénot 2009).

A serious radiological accident occurred in Istanbul, Turkey, in December 1998 and January 1999 when two packages used to transport Co-60 teletherapy sources were sold as scrap metal. The persons who purchased the two packages opened them and broke open the shielded containers. Consequently, they developed acute radiation syndrome. In total, 18 persons (including seven children) were admitted to hospital. Of these, ten adults exhibited clinical signs and symptoms of acute radiation exposure (IAEA 2000a).

2.4.2. Theft of sources

The serious effects that can arise from the theft of a large source are illustrated by an incident in Samut Prakarn, Thailand in 2000. A 15.7 TBq Co-60 teletherapy machine, purchased in 1974 but never used, was stolen by four scrap collectors and rapidly resold. Over the next three weeks, 13 people were exposed. Ten of them were hospitalised for haemorrhages and burns, and three died during the second month following the theft. Overall, about ten people required intensive medical care and some required amputations. Also, a further 44 individuals exhibited symptoms that might have been due to over-exposure (Nénot 2009). An important contributing cause of this accident was that there was no clear or effective end-of-life provision for the source (IAEA 2002). Because there were no provisions for returning the disused source to the manufacturer, the hospital contracted with a local supplier of similar equipment to handle the disused device (including the disused source) and sold it without notifying the regulatory authority. The local supplier did not have satisfactory arrangements for prompt disposal of the source, which was kept in insecure storage (IAEA 2002). In respect of medical treatment, it is notable that exposed individuals reported to hospitals and outpatient clinics, but their original symptoms (diarrhoea, nausea and vomiting) were not initially diagnosed as being caused by radiation exposure (IAEA 2002). Also, there was apparently no adequate biological dosimetry available to assess the probable range of the radiation doses received by the individuals involved (IAEA 2002).

A theft with more limited consequences occurred in Tammiku, Estonia in 1994, when an abandoned, military 1.6 TBq Cs-137 source was stolen from a waste repository and kept in a house for 27 days. During this period, the death of a young man who had kept the source in his pocket before taking it home was attributed to toxaemia. However, when the victim's nephew was found to be suffering from a haematological disorder and burns, the origin of the diseases was discovered (IAEA 1998c, Nénot 2009). Biological

dosimetry, based on scoring dicentric chromosomes, was found to underestimate the dose received by the victim's nephew, indicating its limitations in cases of inhomogeneous irradiation (IAEA 1998c).

2.4.3. Accidental discovery of sources

Abandoned or inadequately secured sources may be discovered by individuals who fail to recognise their nature and the associated hazard. For example, near the village of Lia, Georgia, three woodcutters found two metallic cylinders around which the snow was melting. During the following cold night they used these cylinders (which were thermoelectric generators each containing 1.3 PBq of Sr-90) for heating. After a few hours, all three presented prodromal signs of the acute radiation syndrome and extensive burns appeared within one to two weeks. Nevertheless, the radiological cause of their injuries was not recognised until three weeks later (Nénot 2009). Similarly, in Xinzhou, Shenxi, China, a worker found a 100 GBq Co-60 source in a deep hole in the ground on a site formerly used for the storage of radioactive wastes. He, his father and his brother died after two or three weeks, with their deaths attributed to an infectious disease. It was only after their deaths that the real cause of their injuries was determined, and the source was not recovered until more than two months after its original discovery (Nénot 2009). In Lilo, Georgia, nine servicemen of the Lilo Training Detachment of Frontier Troops developed local radiation-induced skin diseases on various parts of their bodies and a subsequent inquiry established that this was due to the improper and unauthorized abandonment of twelve Cs-137 sources at the Lilo site (IAEA 2000b). The lack of documentation relating to the plant suggested that there had been only limited contact between the former owners of the sources and the current operating organization (IAEA 2000b).

2.4.4. Entry into high dose-rate areas

In some contexts, individuals may decide to enter high dose rate areas to remediate fault conditions. For example, at an industrial irradiation facility near San Salvador, repackaged medical products were sterilized by irradiation using an intensely radioactive Co-60 source in a movable source rack. The accident happened when this source rack became stuck in the irradiation position. The operator bypassed the already degraded safety systems and entered the radiation room with two other workers to free the source rack manually. All three workers were exposed to high radiation doses and developed the acute radiation syndrome. Although their initial hospital treatment was effective in countering the acute effects, the legs and feet of two of the three men were so seriously injured that amputation was required. Moreover, the worker who had been most exposed died six and a half months after the accident, his death being attributed to residual lung damage due to irradiation, exacerbated by injury sustained during treatment (IAEA 1990). This accident illustrates the potential significance of allowing both physical protection and safety procedures to progressively degrade (IAEA 1990). This accident happened in 1989 and the following year a similar accident occurred at a commercial irradiation facility at Soreq, Israel. In this accident, only one operative entered the irradiation room. He received a whole-body dose of between 10 and 20 Gy, and died, because of haemopoietic and gastrointestinal effects, 36 days after the exposure (IAEA 1993). A similar accident occurred in an irradiation facility in the town of Nesvizh, Belarus in October 1991 (IAEA 1996a). An accident with more limited radiological consequences occurred in Hanoi in 1992, in which an individual adjusted the position of a sample at an electron accelerator without being aware that the beam was switched on for part of the time that he was near the sample. During the sample repositioning, his hands were within 0.03–0.3 m of the target. Consequently, he experienced severe injuries to both of his hands, and one had to be amputated (IAEA 1996b).

2.5. Malicious activities

Both sealed and unsealed sources may be used maliciously to cause injury or death. Two attempted murders in the 1970s involved the use of radioactive sources. In one, a man deliberately exposed his son to a 37 GBq Cs-137 source that he was holding for oil prospecting and in the second a reprocessing plant employee, intending to cause severe injuries to a colleague, placed under a car seat a radioactive bar that he had stolen from a workshop. A Russian publication reports at least four criminal actions involving gamma sources (Krasniouk 2004, Nénot 2009). More recently, Po-210 was used in the poisoning of Mr Alexander Litvinenko (Harrison *et al* 2017a), which led also to collateral contamination of other individuals, including eight that received effective doses in the range of 10–100 mSv (Harrison *et al* 2017b).

3. Approaches to medical management

Valentin and Stenke (2022) have set out a proposed reading order for the papers included in the Special Issue. This has been broadly followed in the following discussion.

3.1. Trend in high-dose exposures

Holmberg and Pinak (2021) emphasise that currently most high-dose exposures seem to occur in the medical uses of radiation and that there is a trend for the numbers of such high-dose exposures to increase with time. They present arguments that radiotherapy may result in about 300 events worldwide each year involving significant over-exposures but recognise that not all of these will result in clinically significant effects. In the context of interventional fluoroscopy, they present arguments suggesting that two hundred to two thousand radiation injuries may arise globally each year from this modality. Some of these injuries may be unavoidable because of the nature of the investigations being undertaken, but many may be preventable and Holmberg and Pinak (2021) argue that increased attention to protection of the patient in these situations would be warranted and that systematic follow-up of patients who have undergone high-dose radiation exposures needs to be strengthened. Such follow-up would support an increased understanding of the effects of partial-body irradiation in inducing clinically adverse effects. Although such understanding would focus on specific irradiation regimes, it is likely that it could be generalised to develop a more widely applicable model for the effects of partial body irradiation that could be applied in other contexts, e.g. accidents arising from the use of sources in industrial radiography. Overall, the development of such a generally applicable model should be a research priority in the context of medical management of radiation injuries.

3.2. Approaches to triage

Lebaron-Jacobs and Herrera-Reyes (2021) also address the likely frequencies of radiation accidents and the potential occurrence of terrorist incidents involving radioactive materials, but their focus is more on the triage of accident victims and their subsequent medical management. They emphasise that the priority must be on handling life-threatening situations, and that addressing issues relating to radiation exposure or radioactive contamination should be a secondary consideration. There are good reasons for this. Only at very high short-term radiation doses (tens of gray of whole-body dose) are clinical effects manifest on timescales of minutes and individuals receiving such doses have no possibility of survival. At lower, whole-body doses, where delivery of the dose is protracted, and where inhomogeneous, partial-body irradiation occurs, there is a window of opportunity of hours to days in which treatment of the developing consequences of radiation exposure can be initiated. Lebaron-Jacobs and Herrara-Reyes (2021) suggest, rightly in my view, that, in mass-casualty situations, initial triage must be made rapidly and with limited clinical information. Furthermore, decisions may need to be made by individuals with little or no clinical experience of radiation injuries or radioactive contamination. Therefore, a simple, three category, system of triage is proposed:

- Victims who have been over-exposed or are suspected of over-exposure and present with signs of trauma: these should be managed as a medical emergency,
- Victims who have been exposed externally or internally: this group should be routed to a treatment centre for secondary triage into three subgroups (whole-body exposure, local exposure of parts of the body, contamination with radionuclides),
- Victims who have received low doses and are free from any other injury who should be registered and controlled as outpatients for a few days.

Although it is sensible to adopt a simple triage system, the scheme would need to be adapted to specific contexts and potential types of incidents. For example, if the main concern is with accidents that could result in releases of aerosols of plutonium or highly enriched uranium from on site fires or chemical explosions, secondary triage is unlikely to be needed as the focus would be on individuals subject to external and internal contamination, with a specific emphasis on identifying those who might have inhaled a substantial amount of the radioactive aerosol. Also, victims with trauma might be restricted to on-site personal, who could be handled differently from members of the public.

It might also be useful to define a fourth group comprising those with such low levels of exposure or contamination that they do not require further follow-up. This could be of particular importance for incidents in which large numbers of unexposed individuals suspect that they may have been exposed and require reassurance monitoring. This could occur, for example, where populations know that they are resident in zones covered by off-site emergency plans and, therefore, suspect that they may be exposed or contaminated if an off-site incident is announced. In this context, it is important to recognise that the consequences of accidents and incidents include both psychiatric and psychological illnesses such as depression, anxiety, post-traumatic stress disorder and various somatic symptoms, as well as behavioural disturbances. Furthermore, these consequences can have long-term persistence. Therefore, planning for accidents and incidents needs to include provision for psychosocial care and high quality, trusted risk communication (Lindberg *et al* 2022).

Initial triage will usually be based on clinical observations plus information on the nature of the accident and the location of the victim. Subsequently, simple data from contamination monitoring is likely to become available and, in the longer-term, various measures of radiation exposure and of the likely response of the victim will become available. The various measurements that may be acquired and their interpretation are addressed by Blakely *et al* (2021). They emphasise that dose estimation may be of limited value in determining risks to health and appropriate approaches to treatment, particularly in most cases in which irradiation is to only part of the body or is substantially inhomogeneous. Instead, they recommend a combined use of biological, clinical and physical dosimetry to provide an early phase diagnostic guide to medical management, but complemented by observations of clinical signs and symptoms, blood chemistry biomarkers and cytogenetics to predict acute radiation injury severity. An important message here is that an excessive focus on dose estimation can be a distraction from using more directly relevant data to judge the clinical status of the victim. In this context, they introduce the medical treatment protocol (METREPOL) database of cases that provides early phase clinical signs and symptoms. Data from victims of an incident can be compared with information in this database and used to accurately predict the likely severity of the acute radiation syndrome that will arise. In view of developments of Artificial Intelligence (AI) in other areas of clinical diagnosis and radiological protection, it seems likely that the METREPOL database, enhanced with additional cases, as they arise, could be used to further enhance the scope and predictive accuracy of the software tools that have been developed for predicting the likely severity of radiation injuries in the victims of incidents and accidents. Furthermore, as discussed by Lebaron-Jacobs and Herrara-Reyes (2022), the METREPOL protocol is now twenty years old and although it still constitutes a useful clinical decision tool, there is a need to update it to include new information on the pathophysiological mechanisms of radiation-induced damage, advances in diagnostic techniques and new therapeutic strategies, and possibly to extend its scope beyond the assessment of haematological, neurovascular, cutaneous and gastrointestinal damage (see also Stenke *et al* 2022).

Lamkowski *et al* (2021) examined the effectiveness of various diagnostic tools in training students in the diagnosis of acute radiation syndrome. The exercise scenario simulated a radiological exposure device resulting in potential radiation exposures of 191 people. Clinical signs and symptoms were created from medical treatment protocols in the METREPOL database and from real case descriptions. Normal values of physiological characteristics were also used to represent 89 people without radiation exposure, because 'worried well' individuals together with significantly exposed individuals may require triage. Both on-site and on-line teaching resulted in accurate predictions of response categories, clinically significant acute radiation syndrome, and need of hospitalisation. However, on-site training was found to result in more accurate diagnoses and gave twice the rate of evaluation of cases. Therefore, on-site training is currently preferred, though there may be room for improvement in on-line training to enhance its accuracy and efficiency.

3.3. Biomarkers

Balajee *et al* (2021) considered the cytogenetic markers that can be used in the biological monitoring of radiation-exposed humans. The classic approach is to score dicentric chromosome aberrations in peripheral blood lymphocytes but scoring of translocations (involving the exchange of fragments between two or more chromosomes) can also be useful, bearing in mind that reciprocal translocations can arise spontaneously, and their baseline frequency appears to be modulated by confounding factors such as age and lifestyle. Additionally, chromosome-banding techniques permit the identification of intra-chromosomal exchanges as well as inter-chromosomal exchanges.

As Balajee *et al* (2021) point out, it is convenient to use markers of health impact derived from blood cells because blood can be obtained in a minimally invasive manner, and white blood cells are both extremely sensitive to radiation and ubiquitously distributed throughout the body. However, the disadvantage of using blood cells is that they do not readily distinguish between whole-body uniform irradiation and part-body or inhomogeneous irradiation, i.e. they indicate only an average level of whole-body irradiation, with the nature of the average determined by the shape of the dose-response relationship. To some degree, this deficiency can be overcome by studying the statistical distribution of numbers of the marker aberration between cells, e.g. number of dicentric aberrations between cells. A distribution that is over-disperse compared with a Poisson distribution is indicative of heterogeneous exposure but does not provide information on the spatial distribution of that heterogeneity.

Although scoring of dicentrics and translocations remains the mainstay of cytogenetic dosimetry, other markers can also be used. Balajee *et al* (2021) identified the Pseudo Pelger-Huet (PH) anomaly as a useful marker. PH cells are a subset of neutrophils that are characterised by a bilobed nucleus connected by a thin chromatin filament. Pseudo-PH cell numbers are increased by exposure to ionising radiations and their numbers can be correlated with the dose received. A more direct indicator of the acute radiation syndrome is the neutrophil to lymphocyte ratio, which is an indicator of damage to the haemopoietic system and may,

therefore, be useful as a triage tool for assessing the likelihood of occurrence of the acute radiation syndrome in an individual without going through the intermediate step of estimating the dose received (Balajee *et al* 2021). Other indicators include lymphocyte depletion kinetics and various proteomic biomarkers (see section 4.4 of Blakely *et al* 2021). Specifically, measurement of lymphocyte depletion kinetics is a very common test in everyday healthcare and could, therefore, should be useful in triage (see EBMT 2017). Abend *et al* (2022) emphasise the potential usefulness of molecular protein or gene expression biomarkers for high-throughput and point-of-care diagnosis in the first few days following a radiation accident. They also note that the various potential markers respond differently in relation to characteristics such as radiation quality, dose and dose rate. This suggests that measurements of multiple markers are likely to be appropriate, and AI techniques are likely to be useful in interpreting the complex signatures that arise, particularly if large numbers of accident victims need to be triaged.

3.4. Treatment modalities

If excessive exposure to ionising radiation has occurred and an evaluation has been made of the dose received and, more importantly, of the type, extent and degree of adverse effects that are likely to arise in consequence, the next consideration is what medical measures should be adopted to mitigate those adverse effects. If the classic acute radiation syndrome is predicted to occur, e.g. due to relatively uniform whole-body irradiation, it seems reasonable to treat the destruction of haemopoietic stem cells associated with this syndrome by the use of haematopoietic cell transplants to support haemopoiesis pending recovery of function by the haemopoietic system of the patient. This approach was attempted following the Chornobyl accident by Gale, who describes the results and his conclusions from that attempt and subsequent work in Gale (2021). After the Chornobyl accident, 13 persons exposed to estimated whole-body doses of 5.6–13.4 Gy received bone-marrow transplants. Two transplant recipients who received estimated whole-body doses of 5.6 and 8.7 Gy are alive more than 30 years after the accident with recovered endogenous haemopoiesis. The others died of diverse causes including burns, interstitial pneumonitis, graft versus host disease, acute renal failure and respiratory distress syndrome. There was haemopoietic recovery in nine of these individuals, but graft versus host disease was diagnosed in four individuals and suspected in two others. Overall, Gale (2021) now considers that, if there is a role for haematopoietic cell transplants in radiation accident victims, it is very limited. Specifically, it should only be considered when the whole-body radiation dose is more than 10–12 Gy, but only then when it is considered that bone marrow failure will be the proximal cause of death and it is also considered that the victim has a reasonable probability of surviving damage to other organs and tissues from radiation and other toxic exposures. To this should be added the further consideration that transplants would not be appropriate if only part of the victim's haemopoietic system has been irradiated. In these circumstances, endogenous haemopoietic function will be sustained and the effect of a bone-marrow transport would not only be unnecessary but would carry a high risk of graft versus host disease (see also Gorin *et al* 2006).

Samoylov *et al* (2021) provide a wider perspective on individuals who developed acute radiation syndrome following the accident at Chornobyl. Of 134 patients, 28 died within 100 days after exposure, with radiation skin lesions being the cause for 19 of them. An emphasis of their review is the need to provide long-term support to individuals who develop the acute radiation syndrome and that long-term consequences include late radiation ulcers and radiation-induced fibrosis.

In respect of medical management of individuals subject to heterogeneous, whole-body irradiation, Akashi and Maekawa (2021) present an extremely informative case study of the clinical history of three workers heavily exposed because of the Tokaimura criticality accident. In this accident, Worker B located on a platform was pouring a nitrate solution of enriched U-235 from a bucket into a tank. When this went critical, he was exposed to a high dose of neutron plus gamma radiation, as was Worker A, who was standing on the floor adjacent to the tank. Their supervisor, Worker C, was in the next room, a few metres away and shielded by the wall. Various estimates of whole-body dose to these workers are given in Table 2 of Akashi and Maekawa (2021). These estimates are in good accord with one another. Those based on the specific activity of Na-24 in blood are representative being 19.0, 9.0 and 2.9 Gy for Workers A, B and C, respectively. Although Worker C showed depression in white blood cell and neutrophil counts, reaching a nadir at 20 days after exposure, the counts recovered subsequently and he was able to leave hospital on day 82, but needed subsequent mental health support. Key aspects of his hospital treatment were reverse isolation during bone-marrow depression and administration of granulocyte colony stimulating factor (G-CSF). Both Workers A and B showed severe depression of white-blood cell and neutrophil counts and were treated with haematopoietic stem-cell transplants and G-CSF injections. Although there was recovery of haemopoietic function, Worker A died following a period of massive fluid loss from the skin and bleeding from the gastrointestinal tract and Worker B died because of multi-organ failure. These cases illustrate that there is, at most, only a narrow window of whole-body dose over which complex medical treatments can influence

survival and that, with doses of a few gray, reverse isolation and administration of G-CSF can be key requirements while endogenous haematopoietic function is restored. This conclusion is supported by the review by Lazarus *et al* (2021) who suggest that the weight of evidence favours giving molecularly cloned haematopoietic growth factors (G-CSF and granulocyte-macrophage colony stimulating factor {GM-CSF}) to appropriate persons (those receiving whole-body doses of 3–10 Gy). They also suggest that other supportive interventions, including transfusions of red-blood cells and platelets, anti-microbial, -fungal, and -viral drugs, and burn care are also important in saving lives (see for example the treatment regime described in section 5 of IAEA 2000c). Similarly, Dainiak and Albanese (2022) conclude that an overlap of syndromes develops at higher radiation doses and requires expertise and intervention from multiple specialists. Specifically, management of bleeding and infections are important, and anti-inflammatory drugs may be useful in mitigating multi-organ failure. Control of infections is addressed in detail by Maher *et al* (2021), who emphasise that such treatment should be prompt and individualised and needs to be able to address a wide range of bacterial, viral and fungal infections.

Although not addressed in detail in the Special Issue, it is relevant to note that animal models have a potentially important role to play in assessing the effects arising from various inhomogeneous exposure regimes and the efficacy of different treatments in mitigating such effects. For example, with uniform, whole-body irradiation, it is impossible to evaluate all aspects of the acute gastrointestinal syndrome, because of lethality due to the acute haemopoietic syndrome. However, in animal studies this can be overcome by shielding a fraction of the bone marrow from irradiation. This facilitates not only studies of the acute gastrointestinal syndrome, but also the progression of various delayed effects of acute, non-uniform radiation exposure (MacVittie *et al* 2012). Shielding of the bone marrow also facilitates studies on the effectiveness of various treatments in mitigating the effects of acute, high-dose, inhomogeneous irradiation (e.g. McVittie *et al* 2015). A summary of the role of animal models in developing medical countermeasures (MCMs) to both immediate and delayed effects of acute, high-dose exposures together with extensive references to the relevant literature is given in section 1.2 of MacVittie and Farese (2021).

As discussed in section 2, many radiation incidents result in localised exposures. Specifically, accidents involving sealed sources can result in high doses to the skin. Iddins *et al* (2022) provide a comprehensive review of adverse effects on the skin, many of which were first observed in the late 1890s or early twentieth century. However, modern diagnostic tools, such as imaging by ultrasound and thermography may provide useful additional diagnostic insights to guide treatment, e.g. in respect of dosimetry-guided surgery, which may be complemented by the injection of mesenchymal stem cells into specific areas. Radiation injuries are slower to heal than thermal burns, and pain management is an important consideration. However, although various therapeutic modalities show promise there remains work to be done to bring them into therapeutic use and there are currently no specific drugs approved by the US Food and Drug Administration (FDA) to treat cutaneous or local radiation injury.

The above discussion has focused on the complex of adverse effects that can arise solely because of exposure to ionising radiation. However, in some contexts, e.g. accidents when using glove boxes or the explosion of dirty bombs, high doses of radiation may occur in conjunction with mechanical injuries. Furthermore, the mechanical injuries may also be associated with radioactive contamination. Some of the issues in addressing combined effects are addressed by Glowacki *et al* (2021) who use a mouse model to demonstrate dose-dependent impairment of wound healing with later recovery. They also showed how single doses of various drugs could be useful in mitigating delays in the healing of bone injuries. However, as Glowacki *et al* (2021) comment, combined injuries and their mitigation have not been extensively researched. Because such studies necessarily involve the inflicting of wounds on experimental animals, careful thought needs to be given to designing a research programme in this area that is optimised to yield the maximum amount of useful information for emergency planning purposes while limiting the number of animals used and the stress to which they are subject. In this context, Glowacki *et al* (2021) emphasise that their work was conducted using the protocols of their Institutional Animal Care and Use Committee.

The use of animal experiments in developing MCMs is also addressed by MacVittie and Farese (2021). Under the US FDA rules, approval of an MCM when human studies are not ethical or feasible requires use of well-characterised animal models, with the effect demonstrated in more than one species in respect of an endpoint that is clearly related to the desired benefit in humans and with pharmacokinetic and pharmacodynamic information sufficient to allow selection of an effective dose to humans. To date, only four MCMs have been approved. These all relate to the stimulation of leucocyte growth or the hastening of neutrophil recovery, i.e. they are directed to addressing the haemopoietic acute radiation syndrome and typically required a decade or more to achieve approval for use in humans. There are no MCMs relating to other syndromes, such as those relating to the gastrointestinal tract and skin damage, with associated extreme loss of fluids and internal bleeding, as discussed above in relation to the Tokaimura criticality accident (Akashi and Maekawa 2021). MacVittie and Farese (2021) call for the development of a coherent

approach to the selection and application of animal models, with a view to minimising the use of animals. The requirements for using more than one species and of ensuring that the results obtained can be applied quantitatively to humans is particularly challenging. Although studies on small animals, notably mice, are informative, the requirements mean that some studies are likely to be required in non-human primates. Overall, attention needs to be directed to ensuring that the animal models adopted are well matched to the MCMs being studied, that the use of animals is as limited as possible, considering the need to obtain useful results, and the requirement to ensure that the mix of animal models adopted minimises the use of non-human primates.

Once MCMs have been approved, they need to be integrated into overall plans for emergency preparedness. To facilitate such incorporation, it is desirable that the MCMs have long shelf lives and can be stored at room temperature. Also, although MCMs designed specifically for treating acute radiation exposures may be useful and stockpiled on a buy and hold basis, it is advantageous if they have other, commercial applications, in which case supplies may be managed through a vendor- or user-managed inventory (DiCarlo *et al* 2021).

With respect to the treatment of radioactive contamination, Laurent and Florence (2021) have reviewed methods for determining internal contamination and estimation of internal dose. They also give some attention to decorporation techniques including the use of chelation agents calcium-diethylenetriamine pentaacetate and zinc-diethylenetriamine pentaacetate (Ca-DTPA and Zn-DTPA), blocking agents (e.g. KI) and Prussian Blue ($Fe_4[Fe(CN)_6]_3$). For handling of contaminated wounds NCRP Report No. 156 (NCRP 2006) remains an invaluable reference.

Turning from the medical management of victims of accidents or deliberate misuses of radioactive materials, consideration needs to be given to the management of individuals exposed to high doses of radiation in medical practice. As Holmberg and Pinak (2021) emphasise, currently most high-dose exposures seem to occur in the medical uses of radiation. In this context, there are specific concerns over the adverse effects that may arise when pregnant women are irradiated. This is addressed by Applegate *et al* (2021), who note that high dose radiation exposure of pregnant patients is generally avoided, but can, in some cases, be unintentional or unavoidable. Legitimate reasons include diagnostic imaging for trauma, image-guided interventional procedures and radiotherapy for cancer. In addition, unintended doses to the embryo or fetus can arise if external irradiation or a nuclear medicine examination takes place in circumstances in which the pregnant status of the patient has not been recognised. From a review of the literature, Applegate *et al* (2021) conclude that there are three main considerations in evaluating potential adverse effects on the irradiated embryo or fetus. These are severe foetal malformations or death, future cancer risk, and future impacts on cognitive function. These effects have been known for many years and although it would be useful to obtain more data to quantify the dose-response relationships with which they are associated, enough is already known to mean that further research on this topic is not a high priority.

A specific medical context in which doses high enough to cause severe adverse effects are deliberately administered is addressed by Lindberg and Onjukka (2021). They describe the use of stereotactic body radiation therapy (SBRT) for controlling tumours located close to central thoracic structures. In this technique, an ablation dose of 7–18 Gy per fraction is delivered to a small target volume, with only a small number of fractions employed. For ultra-centrally located tumours, adverse effects are more extreme than for moderately centrally located tumours. In the case of ultra-centrally located tumours, high-grade/severe toxic effects have been reported to occur in up to 55% of treated patients, with up to 22% of patients suffering fatal events that may have been related to the treatment. This study illustrates that the topic of accident and incident management can be informed by results from clinical practice, particularly if work is conducted to improve that clinical practice by elucidating the mechanisms by which severe adverse effects are induced by such therapeutic modalities, and to identify medical treatments that may be used to mitigate these effects. This approach would be complementary to the use of animal models in developing MCMs.

Because therapeutic procedures involve the administration of high doses to normal tissues as well as the tissues and organs that are the target of treatment, there is concern that cancers will be induced in consequence. Where the treatment relates to an existing cancer, such induced cancers are described as second primary cancers. The potential for induction of such second primary cancers has been reviewed by Wakeford and Hauptmann (2022) who concluded that the risk of such cancers varies with the tissue that is exposed and, except for a turndown of the risk of cancer of the thyroid, increases linearly with increasing cumulative tissue dose over a dose range of tens of gray. However, the excess relative risk per gray varies with cancer type and is notably less than that experienced by the Japanese atomic bomb survivors who received moderate-to-high whole-body doses. This emphasises the need to optimise treatment regimes with the aim of maximizing the probability of achieving a cure while minimizing the risk of inducing adverse effects.

At low doses and dose rates, it is usual to consider that the main effect of exposure is the induction of fatal or non-fatal cancer. However, at higher, chronic levels of exposure, it has been proposed that a broadly

characterised chronic radiation syndrome (CRS) occurs. CRS was first described in the 1950s in Mayak PA personnel and involved tissue reactions primarily in the haematopoietic, immune and nervous systems, with dose-dependent suppression of haemopoiesis the leading clinical characteristic. Subsequently, CRS has been identified in the population of settlements on the floodplain of the Techa River who received an average bone marrow dose of 0.35 Gy, with individual values ranging up to 7.92 Gy. Akleyev (2021) gives an account of the medical care provided to members of this population diagnosed with CRS. Medical care has been symptomatic in nature, with a main focus on the recovery of haemopoiesis, which could include the transfusion of blood components in cases of bone marrow hypoplasia.

4. Conclusions

Accidents and incidents giving rise to high radiation doses may involve over-exposure of a single individual, as in many of the reported incidents involving sources used for industrial radiography, a few individuals, as in the criticality accident at Tokaimura, or very large numbers, as at Chornobyl or as could arise from explosion of a dirty bomb or nuclear device. In general, these exposures will be relatively short-term, ranging from a few seconds to a few days, but chronic situations resulting in high exposures can occur, as in the settlements along the Techa River. Some of these exposures may be highly localised, whereas others may result in almost uniform whole-body irradiation. Special considerations arise in therapeutic uses of radiation, where inhomogeneous irradiation is required, but normal tissues are necessarily irradiated to some degree. This diversity of situations means that it is not feasible to have a single protocol for the diagnosis and treatment of over-exposed individuals.

If the over-exposures are limited to one or a few individuals, these can be addressed on a case-by-case basis. However, where large numbers have been exposed or may have been exposed, there is a need to implement a rapid and effective system of triage. Furthermore, this system is likely to have to be implemented by individuals who have little or no direct experience of radiation-induced injuries. Effective triage can be achieved in such circumstances if suitable diagnostic software is available to handle and evaluate the limited information that will be available, and if the staff who would be responsible for triage are trained in the use of the software using synthetic case data, e.g. based on the METREPOL database, or an extended version of it.

In planning resourcing for a potential incident involving the possible exposure of large numbers of individuals, it should be recognised that the number of people requiring reassurance monitoring may be much larger than the number significantly exposed. Furthermore, it is advisable to adopt an approach to triage that does not require follow-up with these individuals in the period following the incident, thus freeing-up resources for more urgent activities.

For those individuals who may have been significantly exposed, the key consideration is not to determine the radiation dose that they have received, but to establish their present clinical status and how it is likely to develop with time. It is this information that will determine the medical management option to apply. Furthermore, arrangements should be in place to update that evaluation of clinical status and modify the medical management option accordingly. In evaluating clinical status, simple observations should be complemented by taking samples to evaluate both the radiation dose received and physiological changes, e.g. in blood cell concentrations, of prognostic relevance. Additionally, where localised irradiation has occurred other techniques, such as imaging by ultrasound or thermography, may be useful.

Sampling of blood is likely to remain fundamental to evaluations of clinical status. However, there is a need to consider the full range of biomarkers that can be used. These range from gross chromosomal changes to indicators of gene expression and encompass measures such as changes in concentrations of different types of cells. Because these various markers respond differently, depending on the characteristics of the radiation field, the use of multiple measures has the potential to elucidate detailed characteristics of the exposure situation that may, in turn, inform medical management. With a proliferation of available markers and the potential to evaluate their heterogeneity of expression in individual cells, it may be helpful to develop AI techniques for their interpretation. This could have the twin advantages of speeding up interpretation, and of increasing the accuracy and repeatability of such interpretation.

However, there is a possibility that focusing on analyses based on blood samples could mean that insufficient attention is given to the spatial inhomogeneity of exposure and could over-emphasise risks of the haemopoietic syndrome at the expense of neglecting the possibility that effects on the gastrointestinal tract or skin might be the key determinants of longer-term clinical status.

In respect of treatment, it is clear that there is at most a very limited role for bone-marrow transplantation in the treatment of acute radiation syndrome, whereas there are good arguments for administering G-CSF and GM-CSF together with other supportive interventions, e.g. in control of infections and handling both fluid loss and bleeding. As noted by Stenke *et al* (2022) the US FDA has licensed G-CSFs and GM-CSFs, as well as romiplostim (a thrombopoietin), to boost bone marrow function and increase

survival in patients acutely exposed to myelosuppressive doses of radiation. However, there is concern that the US FDA has licenced only drugs related to the management of haematopoietic effects. This is particularly important because of the long lead time for licensing new drugs. Because human studies will not, in general, be ethical or feasible to test these drugs, animal models will have to be used and these are likely to involve some studies on non-human primates. This will require careful consideration by ethical committees to make sure that such studies are appropriately justified and optimised. It is possible that medical practice may be relevant as a supplementary source of information, with techniques developed to limit adverse effects in high-dose treatment regimes such as SBRT of potential applicability in accident contexts.

Overall, although a great deal is known about the diagnosis and treatment of injuries arising from high dose exposures, this knowledge is biased towards situations in which there is relatively uniform, external whole-body exposure. In the future, more attention needs to be given to expanding and systematising our approach to assessing the implications of various inhomogeneous exposure regimes arising from incidents and accidents (and in medical practice), and to developing MCMs optimised for addressing the complex, multi-organ effects likely to arise from such inhomogeneous exposures. In this context, appropriate use of animal models will be required.

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Conflict of interest

This research received no grants from any funding agency in the public, commercial and not-for-profit sectors.

Ethical Statement

This research is based solely on a review of published literature. The paper considers ethical issues arising from the use of animals in experimental procedures but does not propose any specific approaches or recommend any guidelines.

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