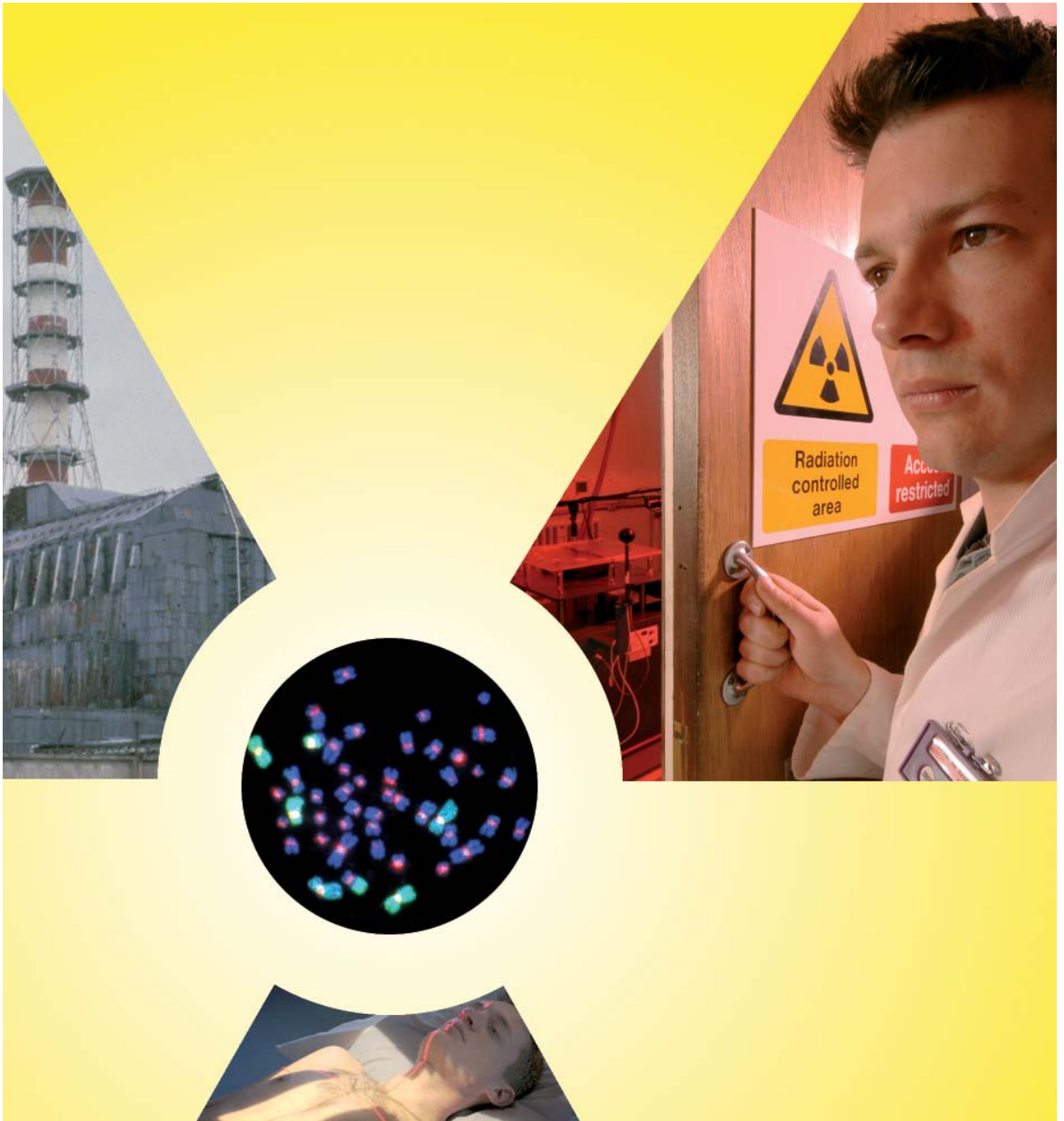


High Dose Radiation Effects and Tissue Injury

Report of the independent Advisory Group on Ionising Radiation



RCE-10

High Dose Radiation Effects and Tissue Injury

Report of the independent Advisory Group on Ionising Radiation

Documents of the Health Protection Agency
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Foreword

The Radiation Protection Division of the Health Protection Agency (HPA) undertakes research to advance knowledge about protection from the risks of ionising and non-ionising radiations. It provides laboratory and technical services, runs training courses, and provides expert information. It also has a statutory responsibility for advising UK government departments and those with regulatory responsibilities for ionising and non-ionising radiations in the fields of medical, public and occupational exposure.

The HPA Radiation Protection Division was formed when the National Radiological Protection Board (NRPB) merged with the HPA on 1 April 2005. In 1995 the Director of the NRPB had set up the Advisory Group on Ionising Radiation (AGIR) that had as its terms of reference:

'to review work on the biological and medical effects of ionising radiation relevant to human health in the occupational, public health, medical and environmental fields and advise on research priorities'

In addition, the AGIR was given the task of helping the NRPB, where appropriate, to deal with any urgent request for advice or work from the Department of Health or other government departments. The AGIR was reconstituted in 1999 as an independent body and reported directly to the Board of the NRPB; since April 2005 it reports to the HPA Board Subcommittee on Radiation, Chemical and Environmental Hazards. The remit of the AGIR is restricted to the provision of scientific judgements and does not include the development of specific recommendations relating to radiation protection policy. These are matters for the HPA and its Board. For details of the current work of the AGIR, see the website at www.hpa.org.uk.

The AGIR has to date issued five reports that consider

- a heterogeneity in response to radiation,
- b guidance on promotion of further optimisation of medical exposures,
- c epidemiology of second cancers,
- d UK population risks for leukaemia,
- e review of risks from tritium.

This report is based on work conducted by the AGIR Subgroup on High Dose Radiation and Tissue Effects. The report reviews the scientific and medical evidence of the effects of exposure to high doses of ionising radiation and what health detriment these effects bring about. It also considers the available treatments and other actions available to ameliorate such effects. Uniquely the report also considers the psychological effects in both those exposed to high doses of radiation and those who may be called upon to treat the exposed people.

High Dose Radiation Effects and Tissue Injury

HAS BEEN PREPARED BY THE

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High Dose Radiation Effects and Tissue Injury

Report of the independent Advisory Group on Ionising Radiation

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1 Introduction

Research into the effects of acute, high doses of ionising radiation originated soon after the discovery by Röntgen of X-rays in 1895, when the first skin erythema was reported (in an X-ray technician) only a year later. With the advent of cancer radiotherapy in the 1920s high dose effects in normal tissues were studied more closely as these were the effects that set the limits to the size of the therapeutic doses that could be given to patients. Research into acute whole body radiation syndromes was encouraged with the start of the nuclear age in the late 1940s and stimulated further research into related medical therapies such as bone marrow transplantation and skin grafting.

In the 1960s new radiotherapy machines and modalities began to be introduced, which used more penetrating forms of radiation, such as cobalt-60 gamma rays, megavoltage X-rays and even high energy neutrons and protons. Again their introduction stimulated work to understand acute and late radiation effects of high doses on normal tissues, and this continued throughout the second half of the twentieth century in the UK and around the world. However, in the 1990s there was a shift of emphasis in the field of radiobiological research when it was considered that much of the underlying biology behind these effects was well understood.

1.1 Background to the report

The latest large reviews in this field appear to have been conducted some ten or more years ago. The most recent review undertaken by the National Radiological Protection Board, predecessor to the Radiation Protection Division of the Health Protection Agency (HPA), was published in 1996 (see below). In autumn 2005 the Advisory Group on Ionising Radiation (AGIR) decided that it was time to review this field to see what research was currently under way on high dose radiation effects and whether there was a requirement for further work.

To undertake this review the AGIR set up the Subgroup on High Dose Radiation and Tissue Effects with the following terms of reference:

‘Damage to normal tissues is significant following radiotherapeutic treatments, certain newer medical practices and, more rarely, diagnostic radiography. Similar acute radiation effects could occur as a consequence of a radiological or nuclear terrorist incident. NRPB published ‘Risk from Deterministic Effects of Ionising Radiation’ in 1996 [*Doc NRPB, 7(3)*]. Given the heightened concern of terrorist incidents, it is timely to assess the acute and late effects of radiation, particularly in relation to tissue injury. The AGIR Subgroup will review developments in this field and report on risks of tissue injury, possible preventative strategies and therapeutic options. The Subgroup will identify gaps in knowledge and make recommendations for future research.’

The Subgroup held its first meeting on 18 November 2005. At its second meeting (held on 23 June 2006), the Subgroup was made aware of the fact that the Department of Health (DH) had asked the HPA for advice relating to possible medical interventions following a severe radiation accident or incident involving exposure of the public to high doses of ionising radiation. This request stemmed from undertakings at the Global Health Action Group meeting held in Brussels in 2006.

Essentially DH was asking the HPA to advise on what would be the best treatments for acute radiation syndrome and any accompanying trauma such as severe skin burns. For information, it may be of interest to note that the HPA intends to use the Goiânia accident as a baseline assessment for these treatment modalities. The HPA had also been asked to advise on whether the expertise to deal with such casualties currently exists in the UK and at what level of casualty number it would be necessary to ask for international help.

To help with this request the HPA asked the AGIR for advice on what are currently the best medical treatments of casualties who may have been exposed to high doses of radiation. (Interim advice to DH has already been provided by the Subgroup – see the panel.) To do this the Subgroup had to consider a variety of accident and incident scenarios that could give rise to high dose exposures of ionising radiation.

In this review high dose effects were taken to be those large enough to cause tissue injury whether resulting from acute or chronic exposures and whether the effects appear early or late. The effects include the four major exposure syndromes relating to whole body irradiation. In practice this review considered doses of one gray and above and all forms of irradiation source, both low and high linear energy transfer (LET) sources and internal and external sources. Furthermore, consideration was given to both the effects of radiation exposure and the dosimetric aspects of exposure which must be taken into

Interim advice to the Department of Health

In June 2006 the Department of Health approached the HPA for advice on practical elements concerning the equipment and facilities needed to treat patients exposed to radiation and suggested that the AGIR Subgroup on High Dose Radiation and Tissue Effects was a suitable forum to address these questions. After discussions, this process was cleared with the Director of the HPA Centre for Radiation, Chemical and Environmental Hazards (CRCE) and the Chairman of the AGIR, and with the HPA Board Subcommittee that oversees work on radiation and chemicals, to which the AGIR reports. The Subgroup then took this extra work into consideration.

However, early in 2007 it was suggested that interim advice to DH was required prior to the timescale being considered for completion of the Subgroup's full report. On 2 March 2007 a meeting was held at DH which was attended by officials from DH and the HPA and the chairmen of both the AGIR and its Subgroup. At that meeting DH posed certain questions on which it would like immediate advice, noting that this would allow the Subgroup more time to consider its full report. These questions were considered at the meeting of the Subgroup held on 26 March 2007. Advice was made available to DH on 27 April 2007 and this advice is reviewed in the summary and conclusions and recommendations chapters of this report.

account when predicting the development and severity of such effects soon after exposure. Uniquely, a review of the psychological effects that are likely in individuals exposed to radiation is included, as is an examination of the psychological response that may be expected in medical professionals involved in treating exposed individuals. Finally, the current state of the field of high dose radiobiology in terms of the research activity being carried out in the UK has been reviewed and recommendations for further research are made.

1.2 Structure of the report

The report has been written in eight chapters. Following this introduction, which provides an overall background and perspective to the report, is a chapter containing a review of the relevant studies of high dose radiation effects in normal tissues in both humans and animals. This review is drawn from a multitude of sources, including human data gathered during the long period during which radiation has been used as a treatment modality for cancer patients (radiotherapy). Thus almost all of the work relates to partial body exposures.

Chapter 3 explores the known high dose effects that occur following particular medical practices as carried out in the fields of radiology and radiotherapy and is focused particularly on total body irradiation and interventional radiological procedures. Chapter 4 considers the doses and injuries that have been incurred following accidental exposures to high doses of ionising radiation.

Chapter 5 reviews the current methods of treatment used to ameliorate the effects of high doses of ionising radiation in a range of tissues and covers what possible actions may be feasible depending upon the number of casualties involved in a particular irradiation scenario. During the course of this review many documents have been sourced that relate to the diagnosis and treatment of tissue damage from high doses of radiation. The most recent – and what we consider the most helpful – of these sources has been included in an appendix to Chapter 5. Treatment is, of course, a matter of clinical judgement but we hope this document will be helpful to those preparing for the treatment of possible victims of high dose exposure situations.

Chapter 6 is unique to reports of this nature and considers the psychological impact of high dose accidents and incidents on both those exposed and those responsible for the rescue and treatment of the exposed individuals. This chapter also contains recommendations and suggestions on the practicalities that may arise from the processes of evacuation and treatment following radiation exposure and the effects of the types of information made available and of the importance of the actual information sources.

The principal conclusions of the AGIR are given in Chapter 7 and the report finishes with a chapter devoted to recommendations for further work in the field of radiobiology, as it relates not only to radiotherapy but also to the understanding of high dose effects and how they may be treated and/or ameliorated. A section is included on recommendations relating to the psychological effects of exposure to ionising radiation. These are particularly addressed to the Department of Health as the review of psychological effects was not sufficiently advanced when we were approached for interim advice by DH.

2 Radiation Injury to Normal Tissues

The human data on high dose radiation effects come mainly from analyses of the Japanese survivors of the atomic bombings at Hiroshima and Nagasaki, examination of individuals who have received large doses in various radiation accidents, and the experience of total body irradiation in the treatment of lymphomas and leukaemias. Data on high dose effects from radiological practices come from patients undergoing fluoroscopy procedures and tend to be of local effects, mainly on the skin. This is the same experience as that coming from radiotherapy treatment of malignancy where local fields are treated and the high dose effects once again are local, mainly on the skin. For exposure to large doses, such as those in radiation accidents or deliberate exposures, the acute radiation syndrome generally starts within two hours of exposure and the severity is dose and tissue dependent. While local irradiation of a specific tissue produces a localised lesion characterised by that tissue, total body irradiation produces a more generalised syndrome. Development of late effects of radiation exposure is more complex and is determined not only by the damage to parenchymal cells but also by the extent of damage to vascular and other supportive tissues. In this chapter the whole body effects are considered first, followed by the local effects.

Recent review of data relating to whole body irradiation, derived mainly from studies of the Japanese atomic-bomb survivors, suggests that the mean lethal whole body radiation dose required to kill 50% of human beings at 60 days ($LD_{50/60}$) is between 3.25 and 4 Gy in people managed without supportive care and 6–7 Gy when antibiotics and transfusion support are provided (Anno et al, 2003; Waselenko et al, 2004).

2.1 Early mortality

The four important causes of early death as a result of radiation exposure are the haematopoietic, gastrointestinal, cerebrovascular and pulmonary syndromes. A fifth possible cause of early death, the cutaneous syndrome, is considered subsequently as severe skin effects occur at such high doses that it is difficult to envisage severe skin damage from whole body irradiation without fatal doses to the bone marrow, with the exception of exposure to short-range particles or soft X-rays, where the acute cutaneous syndrome can be a major cause of death.

2.1.1 Acute radiation syndrome

The acute radiation syndrome occurs after whole or significant partial body irradiation of over 1 Gy delivered at a relatively high dose rate (Waselenko et al, 2004). The components include the haematopoietic, gastrointestinal and cerebrovascular syndromes, and each syndrome can be divided into four phases: prodromal, latent, manifest illness and recovery or death (Waselenko et al, 2004).

TABLE 2.1 Summary of phases of radiation injury: manifestations of illness as a function of dose delivered at a high exposure rate, indicating the prognosis in the absence of intervention (Waselenko et al, 2004)*

Dose (Gy)	Prodrome	Manifestation of illness	Prognosis (without therapy)
0.5–1.0	Mild	Slight decrease in blood cell counts	Almost certain survival
1.0–2.0	Mild to moderate	Early signs of bone marrow damage	Highly probable survival (>90% of victims)
2.0–3.5	Moderate	Moderate to severe bone marrow damage	Probable survival
3.5–5.5	Severe	Severe bone marrow damage; slight GI damage	Death within 3.5–6 weeks (50% of victims)
5.5–7.5	Severe	Pancytopenia and moderate GI damage	Death probable within 2–3 weeks
7.5–10.0	Severe	Marked GI and bone marrow damage, hypotension	Death probable within 1–2.5 weeks
10.0–20.0	Severe	Severe GI damage, pneumonitis, altered mental status, cognitive dysfunction	Death certain within 5–12 days
20.0–30.0	Severe	Cerebrovascular collapse, fever, shock	Death certain within 2–5 days

* Modified from Walker and Cerveny (1989).

Depending on the absorbed dose, symptoms appear within hours to weeks following a predictable clinical course. The prodromal phase of the acute radiation syndrome with anorexia, nausea, malaise and fatigue usually occurs in the first 48 hours but may develop up to six days after exposure. The period before manifestation of the illness is the latent phase which may be associated with some improvement of symptoms as the person appears to have recovered. This effect is transient, lasting for several days to a month. Symptoms of the manifest illness then appear and may last for weeks. This stage is characterised by intense immunosuppression and if the patient survives this stage it is likely that recovery will occur. Those exposed to supra-lethal doses of radiation may experience all of these phases over a period of hours, resulting in early death. Table 2.1, taken from Waselenko et al (2004), summarises these responses as a function of dose delivered at a high exposure rate.

2.2 Haematopoietic syndrome

Early radiation damage to the bone marrow presents the most immediate threat to life following an acute whole body radiation dose from photons of about 2–10 Gy. The haematopoietic syndrome is seldom seen with partial or whole body exposures below 1 Gy. Whole body irradiation produces severe granulocytopenia with subsequent infection and thrombocytopenia with haemorrhage (bone marrow syndrome). Bone marrow depletion, which occurs after exposure to large doses of radiation, begins with

rapid necrosis and lysis of nucleated cells of the marrow within the first 24 hours of exposure with a nadir at three to five days. At doses of 2–3 Gy the haematopoietic progenitors have a limited capacity to divide and in the weeks following the exposure a haematological crisis occurs characterised by hypoplasia or aplasia of the bone marrow. A subpopulation of stem cells or accessory cells (non-nucleated cells: erythrocytes and platelets) is the most resistant of the haematopoietic cells, presumably because of their largely non-cycling (G_0) state. Neutrophils and platelets show dose-related decreases in concentrations and it is the reduction in these that leads to infection and bleeding which contribute to death.

At low doses of radiation up to 1 Gy the white blood cell count may initially rise and then fall but usually remains within the normal range. At slightly higher doses of around 2 Gy this rise is followed by a fall in the white blood cell count which will reach a nadir somewhere around 20 days. The extent of the nadir and the time that it lasts are dependent on dose. The clinical outcome will be dependent on the severity of the neutropaenia and the longer it continues, the greater the chance of a fatal, overwhelming infection. At higher doses of around 8 Gy the neutropaenia is so severe that infection is inevitable and often leads to the death of the patient.

The platelet count is slower to respond to the radiation exposure because the lifespan of mature platelets is longer in the circulating blood (around eight to ten days). Thus the platelet count may remain within the normal range for the first few days and then, once again depending on the dose, begin to decline with a nadir around 22 days. At high doses the platelet count declines more linearly, reaching a nadir around ten days and at this level haemorrhage and infection are extremely likely and will lead to the decline of the patient.

The lymphocytes are the most sensitive indicators of injury to the bone marrow and lymphocyte count declines through interphase death and rapid lysis. It is estimated that a 50% decline in absolute lymphocyte count within the first 24 hours after exposure followed by a further, more severe decline within 48 hours characterises a potentially lethal exposure.

The median lethal dose for human beings is not precisely known, although several estimates have been published ranging from 2.4 to 7.5 Gy for death through the mechanism of bone marrow failure within 60 days of exposure (Bond et al, 1965). Survival after such whole body irradiation requires renewal of haematopoietic stem cells and production of functional end-cells within a critical time period before the body succumbs to haemorrhage and infection from opportunistic pathogens. The higher values of the estimates of the LD_{50} involved cases where significant medical treatment was administered. With minimal medical treatment involving no more than basic first aid, a value of LD_{50} of 3 Gy has been adopted for acute bone marrow dose (NRPB,1996).

2.3 Gastrointestinal syndrome

Very few human data are available on the gastrointestinal (GI) syndrome. It is known that animals receiving acute doses to the gastrointestinal tract of between 10 and 50 Gy die with signs of the GI syndrome. If a dose of over 20 Gy is sustained, death occurs between four and ten days, which is earlier than death from the haematopoietic syndrome (see Table 2.1). Cancer patients have been given

whole body doses of 10 Gy or more in the treatment of leukaemias and lymphomas as part of bone marrow transplantation protocols, albeit at a lower dose rate.

The symptoms associated with the GI syndrome and subsequent death are attributable to the depletion of gut epithelium and breakdown of the mucosal barrier. These changes result in abdominal pain, diarrhoea, nausea and vomiting, and predispose patients to infection. At doses exceeding 12 Gy the mortality rate of the GI syndrome exceeds that of the haematopoietic syndrome. Severe nausea, vomiting, watery diarrhoea and cramps occur within hours after exposure to high doses, that is over 10 Gy. This is followed by a latent period lasting five to seven days during which symptoms might abate. Vomiting and severe diarrhoea associated with high fever then recur to make up the manifest illness. Bowel obstruction from ileus, dehydration, cardiovascular collapse and electrolyte derangements from fluid shifts, together with anaemia from damage to the intestinal tract and subsequent bleeding, lead to sepsis, acute renal failure and death.

The LD₅₀ for the GI syndrome is not fully known but values of around 6.5 Gy for mouse, 7 Gy for rats and 6 Gy for monkeys have been obtained.

2.4 Cerebrovascular syndrome

Radiation damage to the cerebrovascular system is progressive and, based on its time of expression, develops in three different phases: acute, early delayed and late delayed (Sheline et al, 1980; van der Kogel, 1991; Schultheiss and Stephens, 1992). Transient symptoms usually develop relatively early after irradiation, but permanent and often disabling nervous system damage may develop, progressively, within months to years after exposure to ionising radiation.

The acute cerebrovascular syndrome is generally produced only when the whole body radiation dose exceeds about 50 Gy. The survival time is usually less than 48 hours. Individuals presenting with fever, hypotension and major impairment of cognitive function will most probably have had a supra-lethal exposure. The prodromal phase is characterised by disorientation, confusion and prostration, and may be accompanied by loss of balance and seizures. On physical examination there may be papilloedema, ataxia and reduced or absent deep tendon and corneal reflexes. During the latent period apparent improvement occurs for a few hours and is followed by a severe manifest illness. Within five to six hours watery diarrhoea, respiratory distress, hyperpyrexia and cardiovascular shock can occur. The ensuing circulatory complications of hypertension, cerebral oedema, increased intracranial pressure and cerebral ataxia can bring death within two days.

2.4.1 Radiation-induced encephalopathy

Acute radiation-induced encephalopathy is expressed within days to weeks after irradiation and it is associated with headache, somnolence, nausea and vomiting. It develops mainly due to an increase in intracranial pressure. Early-delayed encephalopathy occurs two to four months after radiotherapy and, in children who receive prophylactic whole brain irradiation for leukaemia, this phase is associated with

somnolence syndrome that improves over days to weeks. Late-delayed encephalopathy develops within months to years after irradiation of the brain either prophylactically for leukaemia in children or for treatment of brain tumours in adults. It is usually irreversible, progressive, with no effective treatment available at present, and has been causally associated with the mortality of radiation-induced injury to the cerebrovascular system.

2.4.2 Radiation-induced myelopathy

Myelopathies induced by irradiation of human spinal cord are subdivided into acute transient radiation myelopathy and delayed radiation myelopathy. Transient radiation myelopathy is characterised by paraesthesia that radiates down the spine to the extremities, often brought on by flexion of the neck (Lhermitte's sign). It presents usually between a few weeks and a few months after irradiation of the spinal cord with a median latency period of 4 months and average duration of 5.3 months (Carmel and Kaplan, 1976).

The latency period of delayed radiation myelopathies ranges from four months to four years (Schultheiss et al, 1984, 1988; Schultheiss and Stephens, 1992). The most significant clinical symptoms of delayed radiation myelopathy are paralysis and altered sensation below the site of the damage, while cerebrospinal fluid pressure is usually normal. Delayed radiation myelopathy is considered to be irreversible and even partial recovery is exceptional. Modification of this lesion by stem cell transplantation in an experimental setting has been reported (Rezvani et al, 2001). The probability of death from radiation myelopathy is approximately 25% at 18 months for thoracic cord injuries and 55% for cervical cord injuries (Schultheiss et al, 1986). Both animal and human data suggest age- and dose-dependency for the latency period for radiation myelopathy – the younger the subject, the shorter the latency period.

2.5 Pulmonary syndrome

The lung is a relatively sensitive organ showing two phases of damage: early pneumonitis and oedema – starting within a few weeks of exposure and lasting up to several months – and long-term changes including the development of fibrosis and loss of alveoli which are replaced by collagen and connective tissue to form a scar. Lungs irradiated by external gamma rays and/or by inhaled radionuclides may show a resultant acute radiation pneumonitis some two to four months later. The symptoms include shortness of breath, fever and non-productive cough. Fatalities from pneumonitis are not expected to occur as a result of uniform external body irradiation because the doses required are much higher than those for the earlier expressing haematopoietic syndrome. However, where supportive or intensive medical treatment is given so that the patient survives the haematopoietic syndrome then pneumonitis may be more important. Estimates of LD₅₀ for pneumonitis of about 10 Gy have been made (NRPB, 1996). Experience with interstitial pneumonitis following bone marrow transplantation with total body irradiation at low dose rate (Barrett et al, 1983) has suggested a threshold dose of 8 Gy, but that within the range of 8–10.5 Gy the dose rate would significantly affect the incidence.

2.6 Cutaneous syndrome

In the context of whole body irradiation following a nuclear accident, cutaneous injury can occur from thermal or radiation burns and is characterised by loss of epidermis and on some occasions damage to the dermis that may extend deeply into soft tissue, even reaching underlying muscle and bone. Patients presenting with burns immediately after such exposure have thermal rather than radiation burns and the outcome is complicated by the haematopoietic syndrome as a result of bleeding, infection and poor wound healing.

Cutaneous injuries have been experienced regularly by patients undergoing radical radiotherapy for malignancies and in the past from fluoroscopically-guided interventional radiology when the doses of radiation given to the skin were not appreciated by the physicians undertaking the investigations (ICRP, 2001). The time course of such cutaneous reactions is the same for both radiotherapy and fluoroscopy at specific doses.

The earliest response of skin to irradiation is a transient erythema and oedema, which may appear at the time of exposure or within a few hours, resulting from capillary dilatation. The early erythema often indicates a severe evolution (Gongora and Magdelenat, 1986) and it might be of prognostic significance. The severity of erythema is dose related. The erythema then subsides but may be followed by a secondary erythema and dry desquamation at about one to five weeks. This phase of erythema is due to the release of proteolytic enzymes from damaged epithelial cells (Panizzon and Goldschmidt, 1991).

If the dose is higher, say around 40 Gy, then moist desquamation occurs with blistering of the skin. Moist desquamation is histologically characterised by eroded epidermis and leucocyte infiltration. Inflammatory reaction may subside by weeks five to seven. Overall, moist desquamation is a transient reaction caused by depletion of clonogenic epidermal stem cells and may heal within a few weeks by proliferation of the surviving cells in the irradiated region or by the migration of epidermal cells from the adjacent healthy tissues. If there are sufficient surviving cells within the irradiated area then moist desquamation will heal quickly with no secondary structural damage to the dermis.

The timing of the occurrence of moist desquamation is defined by the total turnover time of the epidermal cells exposed to radiation and is not influenced by radiation dose unless exposure is to high radiation doses. These effects are caused by the death of the cells in the basal layer of the epidermis. In the longer term the skin over the radiation burn may heal but it will always lack sebaceous and sweat glands and be very thin, and may be hypo-pigmented with telangiectasia. Earlier denudation of the epithelium, ie shorter than the normal turnover time, can only occur if basal cells, and more specifically post-mitotic supra-basal cells, are killed directly by irradiation, usually after very high dose exposures.

At high doses, late erythema is another phase of skin reaction that manifests around eight or nine weeks after irradiation. This phase of erythema occurs if a substantial dose of radiation is received by dermal vasculature. In contrast to the early erythema that is bright red, this late erythema usually has a bluish appearance and suggests damage to the dermal plexus. This brings about a state of ischaemia and may lead to necrotic skin lesions that develop nine to sixteen weeks after exposure. Beyond one year the skin acquires characteristics of late radiation damage that manifest as dyspigmentation, atrophy, fibrosis and telangiectasia. Dyspigmentation which can be in the form of hypo- or hyper-pigmentation is usually

observed within the first two years. Telangiectasia can manifest as late as nine years after irradiation (Rezvani et al, 1991). In some cases, several years later, a necrotic ulcer which will not heal without plastic surgery may develop. Epilation, either temporary or permanent, can follow interventional radiology and radiotherapy treatment. High dose, localised irradiation of the epidermis, without comparable effects on deeper dermal layers, can only occur as a result of exposure to less penetrating radiation – for example, low energy beta or alpha radiation. In this situation the primary energy absorption will be in the viable layers of the epidermis above the basal layer. The depth of necrosis depends to a large extent on the radiation dose and radiation quality.

For skin sites that do not develop ischaemic dermal necrosis after irradiation, dermal thinning may be a late consequence. Serial measurements of changes in skin thickness in a pig model, using an ultrasound technique (Rezvani et al, 1994), have indicated that the thinning of dermal tissue develops in two distinct phases after single doses of both X-rays and beta radiation. The first phase of reduction in dermal thickness developed between 14 and 20 weeks after irradiation, the second phase after 52 weeks. The mean reduction in dermal thickness in the periods 20–51 weeks and 76–129 weeks after irradiation was related to dose both after strontium-90/yttrium-90 and after thulium-170 irradiation. However, based on skin surface doses the magnitude of the response was less after irradiation with the lower energy thulium-170 source. When radiation dose was expressed in terms of the dose at 900 μm depth, the mid-dermal depth, comparable results were obtained for both radiation energies.

Temporary epilation tends to occur at doses over 15 Gy and permanent epilation after 40 Gy. Radiotherapy given for cancer usually penetrates into the deeper tissues and can lead to fibrosis of the underlying muscle and bone, leading to later osteoradionecrosis. Mortality usually occurs when a substantial area of the body shows moist desquamation. In general, younger people repair and replace skin more effectively than older people – for example, burns of 30% of the skin produce mortality ranging from 0% for people under 20 years of age to 100% for those over 80 years. Those aged 60 years have 50% mortality.

2.6.1 Radiation-induced vasculopathy

The controversy involving the issue of whether the parenchymal or the vascular tissue is the prime target for radiation damage is not unique to the cerebrovascular system. This controversy exists in the study of the effects of ionising radiation on almost every kind of tissue. It must be borne in mind that radiation is an indiscriminate agent that hits every component of the target tissue. It is equally likely to hit both the parenchymal and vascular components of the irradiated tissues. Damage to any component of tissue initiates a series of changes leading to an organ-specific radiation lesion. Therefore there is always an element of parenchymal damage which is augmented by vascular damage. However, the extent of the contribution of different components of tissue in the development of late radiation effects is not fully understood. The degree of importance of each tissue component is determined by its radiosensitivity and its role in preserving the functional integrity of the irradiated tissue. Blood capillaries and sinusoids are the most radiosensitive components of vascular tissue (Fajardo, 1989). This reflects the radiosensitivity of endothelial cells that constitute a major proportion of the capillary wall.

Manifestation of the effects of irradiation on endothelium varies with time after irradiation and the size of blood vessels. An increased cell permeability after irradiation of endothelial cells and before cell death (Stone et al, 1987), irregularity of endothelial cytoplasm, formation of pseudopodia, detachment of endothelium from basal lamina, rupture of plasma membrane, rupture of capillary wall, and loss of entire capillary segment have all been observed after irradiation of different tissues (Phillips, 1966; Fajardo, 1989).

Reduction in the number of endothelial cells lining the walls of blood vessels has been observed after irradiation of mouse mesentery (Hirst et al, 1979), pig skin (Archambeau et al, 1984) and choroid plexus of the rat brain (Calvo et al, 1987). Loss of endothelium results in a reduction of the microvascular network. Dilatation is very common in the remaining microvasculature and when superficially located it can be clinically detected as telangiectasia of skin or mucous membrane. This phenomenon, together with blockage of larger vessels, eventually brings about a state of ischaemia in irradiated tissue (Hopewell et al, 1986) and ischaemic necrosis. This structural damage to the vasculature and loss of functional capability of endothelial cells might initiate the development of arteriosclerosis which is more common following irradiation (Tracy et al, 1974; Conomy and Kellermeier, 1975; Brosius et al, 1981).

2.6.2 Radiation damage to peripheral nerves

The data concerning radiation damage to peripheral nerves come from patients who received radiotherapy for cancer treatment. Overall, data are very scarce as only a relatively small number of patients develop peripheral neuropathy after conventional radiotherapy. However, from the existing data, it can be concluded that the incidence of peripheral neuropathy is directly associated with the total radiation dose. The latent period can be within 5–30 months after irradiation. Some animal studies have shown peripheral neuropathies clustered around 6–18 months after irradiation. Peripheral neuropathy is considered irreversible, although recovery has been reported in some patients. However, it is one of the important limiting factors in intraoperative radiotherapy.

2.6.3 Radiation damage to skeletal muscle

Muscle is a relatively radioresistant tissue in the human body and data involving the effect of irradiation on muscles come mainly from men irradiated for prostate cancer, women for breast cancer, and men and women irradiated for musculoskeletal sarcomas. Incidence of muscle complications (atrophy or weakness) is as high as 58% in breast cancer patients, and between 77% and 100% for muscles of the pelvis in prostate cancer patients; moderate to severe muscle weakness is reported in 20% of patients with soft tissue sarcomas of the limbs. The extent of muscle damage is both dose dependent and related to the time since irradiation. Information on molecular/histological responses of muscular tissue to irradiation comes mainly from animal models. Increased amino acid release, suggesting protein breakdown, has been reported in rats immediately after irradiation. This was followed by increased collagen content, death of myocytes, muscle degeneration and vacuolisation associated with a loss of capillaries. Later progressive changes to muscle are thought to occur as a result of vascular lesions and

ischaemia. The later fibrotic phase is usually associated with an increase in type III collagen and an increase in production of sulphated glycosaminoglycans (GAGs) for up to seven months after irradiation. A two- to four-fold increase in *TGF- β 1* expression was found within three weeks after 35 Gy and for up to one year later.

2.6.4 Impact of radiation damage on development, particularly on infant and fetal exposure

There is considerable evidence that the embryonic neuronal system is highly radiosensitive. There is considerable appreciation now that the sensitivity and division potential of stem cells strongly influence the response of a tissue. There is evidence that the neuronal stem cells in the embryonic brain represent a defined compartment with limited proliferative capacity and that elevated DNA damage may significantly affect the number and potential function of neuronal stem cells. It is striking that patients with deficiency in the repair of DNA double strand breaks, the main lethal lesion induced by ionising radiation, display microcephaly (small heads) simply as a consequence of endogenously arising double strand breaks. The microcephaly is not progressive post birth, demonstrating a window of sensitivity during development. The information available suggests that the embryonic neuronal stem cells incur high levels of double strand breaks from endogenous oxidative damage and that a failure to repair such damage significantly affects neuronal development. Endogenous DNA double strand breaks do not arise frequently. Hence, even low doses of radiation-induced double strand breaks might be expected to have an impact, even in a repair-proficient individual.

Severe mental retardation (25–30 IQ points per gray for children exposed at 8–15 weeks) has been reported in children exposed *in utero* during the Japanese atomic bombings (Schull and Otake, 1986; Otake and Schull, 1998). These and additional studies raise the possibility that the developing embryonic neuronal system is exquisitely sensitive. This possibility would be consistent with the finding that microcephaly is the most marked feature observed in patients deficient in double strand break repair (excluding immunodeficiency which arises because the development of the immune response has a specific requirement for the double strand break repair machinery).

Pregnant mothers may well be amongst those exposed during a major radiological emergency and will have anxieties for the unborn child. If the embryonic brain really represents a highly sensitive tissue, then it is important that this is fully evaluated. Stem cell biology and neuronal biology are advancing areas of research and a priority should, therefore, be given to evaluating how radiation exposure affects the embryonic brain, and particularly the embryonic neuronal stem cells.

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3 Therapeutic Total Body Irradiation and Interventional Radiological Procedures

The clinical uses of radiation include radiology, radiotherapy and nuclear medicine. The majority of radiology and nuclear medicine exposures are dedicated to the diagnosis of disease. Radiotherapy employs ionising radiation to treat patients, predominantly those with malignant disease.

All clinical radiation exposure procedures attempt to give the lowest dose of radiation that is reasonable and effective. In the UK all patients give their informed consent prior to undergoing the radiation exposure procedure for radiotherapy.

In clinical radiology the exposure volume is kept to the minimum acceptable to provide the information required and strict protocols cover the clinical set up and exposure. Radiation exposure from plain films is minimal, while CT scans and screening give higher doses. Screening procedures are more difficult to regulate since in exceptional cases screening may be unexpectedly prolonged with no alternative for the survival of the patient. Radiation doses delivered by radical radiotherapy are usually to small areas of treatment. The dose given, usually over a period of four to six weeks, is calculated to take the normal tissue to its tolerance dose while delivering a lethal dose to the malignancy. Formal and lengthy procedures are in place to compute and check the field arrangement necessary to treat the cancer and records of all radiation exposures are kept.

An extensive check and recheck system minimises errors. Where errors have occurred they have usually been the result of a calculational error in a small number of fractions within a treatment or due to miscalibration of the machine at the time of installation or subsequent overhaul. Records of non-conformities are regularly reviewed in all radiotherapy and radiology departments; however, with so many protocols and so many personnel, without extreme vigilance, there is clearly capacity for errors.

While radiotherapy treatment is usually directed to the tumour or tumour bed and its surroundings, wider field, total body and total skin electron beam radiation may be given. Wider field irradiation causes systemic symptoms to the patient, such as nausea, vomiting and fatigue. Those treated with smaller field irradiation exhibit mainly local toxicity.

3.1 Total body irradiation

Total body irradiation is the systemic treatment of disseminated malignancy using external beam radiotherapy (Wheldon, 1998). It became an established treatment for haematological malignancies in the 1980s and there are increasing indications for treatment of relapsed malignancies for which this has been used (Thomas, 1987). Historically, the most common indication was relapse of acute lymphoblastic leukaemia. It has also been used in myeloid leukaemia, relapsed Hodgkin's and non-Hodgkin's lymphoma, and myeloma, all of which are characterised by radiosensitivity, systemic involvement and a high mitotic

index. Cures in approximately one-third to one-half of patients with acute lymphoblastic and acute myeloid leukaemia are achieved. A wide variety of non-haematological malignancies such as neuroblastoma, small cell lung cancer, Ewing's tumours, rhabdomyosarcomas and peripheral neuro-ectodermal tumours have been treated. In patients with non-malignant diseases such as amyloidosis, subcutaneous panniculitis, systemic sclerosis, Fanconi's anaemia and systemic lupus erythematosus, total body irradiation has been suggested. Leukaemia and lymphoma cells are both radio- and chemo-sensitive. Although there is a major response to chemotherapy, dose escalation to tolerance may leave residual cells, especially in sanctuary sites which are poorly penetrated by chemotherapeutic agents due to lack of vasculature or to chemical barriers. Total body irradiation has the advantage of potentially treating homogeneously the whole body and this can be used in combination with chemotherapy for maximal response.

The radio- and chemo-sensitive bone marrow is acutely affected by this regimen. Since the whole body dose required to effectively irradiate the malignant stem cells is above the median lethal dose, reconstitution of the haematopoietic system either by bone marrow graft or by stem cell replacement is vital. Total body irradiation is intended to kill the remaining malignant cells. In allografts, using unrelated donors, total body irradiation allows engraftment by leaving space in the recipient marrow for donor bone marrow and causes sufficient immunosuppression to prevent graft rejection. Dose escalation has only been made possible by its use in conjunction with chemotherapy conditioning and bone marrow or peripheral blood stem cell transplantation.

The success rate following total body irradiation increases if there is minimal body burden of disease at the time of treatment. The lower doses of radiotherapy achieved to the whole body relative to the localised treatment of solid malignancies relies upon the relative radiosensitivity of the stem cells associated with haematological malignancies.

The major cause of death of transplant patients is relapse of the primary disease. Graft versus host disease (GVHD), infections and treatment-related organ injury can also be fatal. The high incidence of relapse of the disease for which the treatment was given has always suggested that further advantage may be claimed for escalating the dose. However, dose escalation clearly weights the therapeutic ratio towards complications of treatment. To attempt to prevent complications, many internationally accepted regimens of total body irradiation are given in a fractionated manner (Gopal et al, 1999).

3.1.1 Physics and methods

Total body irradiation is usually performed by a two- or four-field technique using a linear accelerator. Patients are placed on a special couch with acrylic glass walls to ensure full dose in the superficial tissues. The physics of total body irradiation and the geometry and dosimetry of the set up are complex, but the regimen used by large centres that are expert in this field is described in the literature (Van Dyke, 1987; Bradley et al, 1991). There is no consensus as to the optimal radiation dose/fractionation regimen or technique employed. As the lungs are the dose limiting organ, techniques and dosimetry should be designed to accurately deliver the dose to this point. Many methods have been devised to attempt to produce a homogeneous dose distribution. Where lung blocks are introduced, electron beam treatment to the chest wall may supplement total body irradiation. Organ shielding can be introduced to reduce the dose to the kidneys by 25%.

As leukaemic cells may not undertake sublethal damage repair, the frequency of the fractionation is relatively unimportant and the treatment can be given once or twice daily at least six hours apart.

The X-ray energy used is usually between 4 and 24 MeV. Higher photon energy increases dose deposition in bone marrow through pair production and backscatter interactions occur in bone. Tissue dose inhomogeneities are reduced with higher energy radiation. Clearly dose inhomogeneities are important since under-dosing any of the bone marrow may allow recurrence of the leukaemia. Patients are usually treated at an increased focus to skin distance and thus at a relatively reduced dose rate. Doses are verified by the use of thermoluminescent detectors during the course of the treatment.

Although it has been suggested that there is a small shoulder to the cell survival curve for leukaemic cells, the injury due to, and toxicity of, the radiation are dependent on the size of the radiation fraction and the dose rate used. A low dose rate (0.05–0.25 Gy per minute) is usually employed when patients are treated with large, single fractions of radiation. A dose of 10 Gy may be given at low dose rate over six to eight hours. Fractionated total body irradiation is considered to be less toxic than a single dose, but also to be less immunosuppressive, which may result in more graft failure or rejections. A commonly used fractionation regimen is 2 Gy spaced by an interval of six hours repeated for three successive days, up to a total dose of 12–14 Gy. Increasing the total body dose may result in greater freedom from relapse of disease but no improvement in mortality due to deaths from complications.

McAfee et al (2002) have described escalated total body irradiation and stem cell transplantation for refractory haematological malignancies describing three dose levels of fractionated total body irradiation. A dose of 2 Gy was given twice daily to a total of 16, 18 or 20 Gy. The addition of cytotoxic therapy was not used and this therefore gives a more appropriate demonstration of unassisted total body irradiation.

3.1.2 Complications

While attempting to treat the whole bone marrow to a homogeneous dose, care must be taken to ensure that other radiosensitive tissues are not lethally damaged. Although total body irradiation is used in an attempt to cure aggressive disease, the morbidity and mortality are as much associated with the complications of treatment as recurrence of the disease.

Pulmonary pneumonitis is one of the more common and lethal complications. All treatment regimens are directed to achieve the lowest and most homogeneous lung dose. Other early complications include cardiac and renal insufficiency, mucosal toxicity, xerostoma, colitis and acute parotitis. Haemolytic uraemic syndrome, veno-occlusive disease and neuro-psychiatric toxicity may occur. Late complications include secondary amenorrhoea, thyroid dysfunction, impaired androgen production, growth retardation and an increased incidence of subsequent malignant disease.

Optimising fractionation dose rate reduces complications. A higher dose rate was independently significant for an increased risk of interstitial pneumonitis (Carruthers and Wallington, 2004). Morgan et al (1996) analysed the incidence of interstitial pneumonitis, in comparing 18 patients who received a single dose of 6 Gy with 90 patients treated with three doses of 3.33 Gy separated by 24 hours. They noted an 18% incidence of interstitial pneumonitis which was not different in the fractionated dose group as opposed to the single dose group.

Delgado et al (2006) found that the administration of total body irradiation as a single high dose of 7.5 Gy was more significantly associated with an increased risk of chronic renal failure than 12 Gy in six fractions or 14.4 Gy in eight fractions. The cumulative incidence of chronic renal failure at two years was 12%.

Age is a strong predictor of complications from treatment, with older patients tolerating radiation exposure less well (Gopal et al, 1999). Most patients, particularly those with acute leukaemia, are usually in the second or third decade of life and the technique is rarely used in patients over 60 years of age. Most centres reserve total body irradiation for patients under 60 years.

3.1.3 Prophylaxis and support

Patients receiving total body irradiation and high dose chemotherapy will experience profound bone marrow suppression for days or weeks until the donor marrow engrafts and produces mature red blood cells, white blood cells and platelets. Pre-transplant investigations include assessment of organ function – lung, cardiac, renal and risk of reactivation of latent infection. During the time of bone marrow depression basic hygiene is vital and antifungal, antiviral and antibacterial prophylaxis is necessary. Support with irradiated blood products, whole blood and platelets is required. In patients receiving allografts, prophylaxis for graft versus host disease with cyclosporin and methotrexate is necessary.

During and immediately following the course of radiotherapy treatment, patients will experience parotitis, diarrhoea, fever, erythema, mucositis and hyperpigmentation. Nausea and vomiting may occur with considerable fluid loss which must be reintroduced.

The use of intravenous and topical mesenchymal stem cells shows promise in improving outcome following radiation exposure (see Chapter 5).

Prophylaxis has been described in some detail here so as to stress the difference between patients receiving these doses of radiation in a strictly controlled environment and radiation exposure in an accident or incident.

3.1.4 Dose assessment

Biological dosimetry, based on scoring chromosomal aberrations in peripheral lymphocytes, can be used before and after total body irradiation. The FISH method was preferred to conventional cytogenetics in a retrospective study and correlation with dose was good (Dossou et al, 2000).

Belkacémi et al (2003) have discussed monitoring residual haematopoiesis after total body irradiation as a model for accidental X-ray exposure. They noted a significant decrease of human mature and immature progenitors in bone marrow and peripheral blood immediately after low dose total body irradiation. The lack of expansion suggested that autografting using bone marrow residual stem cells collected and expanded *in vitro* in cases of accidental whole body exposure may not be practical.

3.1.5 Discussion

There are clearly many differences when comparing the morbidity and mortality of those irradiated in a controlled hospital environment with those exposed in an accident or incident. Patients who have had previous serious or life-threatening illnesses may have increased toxicity as a result of their earlier treatment. They may be more vulnerable to radiation exposure than the general population. However, patients who have total body irradiation are usually of a relatively young age and may include children who tolerate this treatment relatively well. Critically there is little information on the tolerance of a population older than 60 years of age to total body irradiation.

Knowledge of accurate dosimetry allows appropriate treatment. The homogeneity of total body irradiation prevents any patchy survival of stem cells which may take place when exposure to radiation is inhomogeneous – which is more likely in an accident or incident.

The major difference between patient groups and the general population is the known pre-irradiation status of the patient for total body irradiation, allowing appropriate prophylaxis. This is done in a controlled and staffed environment, anticipating the event. Other associated trauma which an accident or incident may produce and very high dose areas are not seen with total body irradiation. Radiation burns to the skin of varying extent and with associated morbidity and mortality may occur in an accident or incident. Major supportive care will be extremely important, particularly since pre-existing medical history and potential infections are previously undiscovered.

There are probably as many differences as similarities between controlled total body irradiation and accidental exposure. The experience of total body irradiation can therefore only be used as a guide.

Further work on the indications for the use of mesenchymal stem cells to promote the healing of radiation-damaged tissues needs to be encouraged and supported.

3.2 Interventional radiology

Interventional radiology is firmly established in modern medicine. An increasing number of therapeutic procedures are performed under imaging-guidance and interventional radiological techniques are rapidly replacing conventional surgery. For example, it is expected that the vast majority of patients with peripheral vascular disease will be treated using endovascular techniques within a few years. More patients with cardiac disease are now managed using interventional cardiological methods rather than open-heart surgery. Even in specialties in which imaging-guided methods have not reached a stage at which they can replace surgery completely, they are sometimes used in combination with images viewed through an operating microscope.

Many interventional radiological procedures involve extended fluoroscopy times. Also, when fine detail is required, it may be necessary to obtain high resolution images during the procedure rather than rely upon fluoroscopy alone. Although in the vast majority of cases the benefits of interventional radiological treatment greatly outweigh the risks of radiation exposure, it is important to ensure that the latter are not underestimated or ignored. The aim here is to review key publications in this field and to summarise their recommendations in relation to radiological protection during interventional radiological procedures.

3.2.1 Magnitude of the problem

Although it is rare for interventional radiological procedures to result in radiation injury, the number of such procedures is so great, and increasing so fast, that the problem cannot be ignored. In the USA in the late 1990s, it was estimated that more than 700,000 interventional radiological procedures were performed annually (Owings and Kozak, 1998; Shope, 2000) and this number is likely to be much larger now. Furthermore, although many procedures are carried out under ultrasound-guidance, the fine detail provided by multidetector computed tomography (MDCT) has resulted in an increasing use of this modality for complex interventions, particularly tumour ablation. The ability of MDCT to provide the interventionist with rapid three-dimensional reconstructions, thus enabling precise localisation of instruments, is a substantial advantage that, in the view of many radiologists, clinically justifies the increased radiation dose. The hope that magnetic resonance imaging might replace CT in this regard has proven unrealistic because it is extremely difficult to produce magnetic-resonance-compatible instruments with the same capabilities as currently available devices.

An important consideration is the increasing number of specialties using interventional radiological techniques. Until recently, most interventional procedures were performed by radiologists and cardiologists. Radiologists have always been trained in radiological protection; more recently, cardiologists have also been required to receive training in this field, although their training is not as extensive as that undertaken by radiologists. However, the volume and range of procedures are now so great that many more specialties are becoming involved in techniques undertaken using fluoroscopic-guidance. For example, many vascular surgeons undertake insertion of thoracic and aortic stent grafts, procedures that involve extensive fluoroscopic imaging. Surgeons do not usually learn the principles of radiological protection during surgical training and rely upon radiographers to apply such principles during the performance of procedures. Furthermore, the lack of familiarity of surgeons with some of the interventional techniques involved may result in prolonged fluoroscopy times, especially during the learning phase immediately after such procedures are introduced.

3.2.2 Risks

The short-term risk to patients is radiation-induced skin damage. Skin changes such as erythema, ulceration, telangiectasia and dermal atrophy occur only when the radiation dose exceeds a certain threshold. Histologically, a minimum number of cells must be damaged to elicit a response, the probability and severity of which increase rapidly when the dose increases beyond the threshold. The inflammatory changes after irradiation are often referred to as radiodermatitis.

Repair of radiation damage occurs at molecular, cellular and tissue levels. Radiation-induced DNA lesions are processed by enzymes within a few hours. At the cellular level, repopulation occurs within days (Molls and Stuschke, 1991; Trott and Kummermehr, 1991). Therefore, the rate of dose deposition is critical to cellular repair. The types of procedures typically associated with skin injury are given in Table 3.1, which is extracted from a report by the US Food and Drug Administration (FDA, 1994a).

TABLE 3.1 Procedures typically involving extended fluoroscopic exposure time (FDA, 1994a)

Radiofrequency cardiac catheter ablation
Percutaneous transluminal angioplasty (coronary and other vessels)
Vascular embolisation
Stent and filter placement
Thrombolytic and fibrinolytic procedures
Percutaneous transhepatic cholangiography
Transjugular intrahepatic portosystemic shunt
Percutaneous nephrostomy, biliary drainage or urinary/biliary stone removal

Table 3.2, which is adapted from Wagner et al (1994), indicates the threshold doses typical of the absorbed doses in skin that are required to cause a particular effect. The effect is dependent on a number of variables other than the cumulative dose in the skin, such as the rate of delivery of the radiation, fractionation of the absorbed dose, age and characteristics of the person exposed, and site on the skin of the exposure.

The absorbed dose rate in the skin from the direct beam of a fluoroscopic X-ray system is typically between 0.02 and 0.05 Gy min⁻¹ but may range from 0.01 to more than 0.5 Gy min⁻¹, depending on the mode in which the fluoroscopic equipment is operated and the size of the patient. The times required to deliver the typical threshold doses shown in Table 3.2 are for fluoroscopic dose rates of 0.02 Gy min⁻¹ (third column) and 0.2 Gy min⁻¹ (fourth column). In that portion of the skin irradiated by a stationary, continuous fluoroscopic X-ray beam, these are, respectively, the usual or typical dose rate for normal fluoroscopy for an average-size patient and a dose rate near the maximum that would be permitted for high level exposure under a federal limit established in the USA (FDA, 1994b). Thus, even typical dose rates can result in skin injury after less than one hour of fluoroscopy. For comparison, the absorbed dose to the skin from a typical diagnostic X-ray examination is hundreds to thousands of times smaller than the threshold doses for skin injuries given in Table 3.2.

Many fluoroscopic X-ray systems used for interventional radiological procedures operate in such a way as to result in dose rates significantly exceeding 0.02 Gy min⁻¹, which was used as an example in Table 3.2. Many currently used systems can deliver dose rates exceeding 0.2 Gy min⁻¹. Furthermore, during many interventional radiological procedures digital images are acquired in order to permanently record particular aspects of the procedure. The recording modes typically involve much higher dose rates than fluoroscopy and the contributions from fluorography must also be included in assessing the total absorbed dose to the skin. Fluoroscopic systems that are adjusted improperly or have dose rates

TABLE 3.2 Radiation-induced skin injuries

Effect	Typical threshold absorbed dose (Gy)	Hours of fluoroscopic 'on time' to reach threshold* at:		
		Usual fluoroscopic dose rate of 0.02 Gy min ⁻¹	High dose rate of 0.2 Gy min ⁻¹	Time to onset of effect [†]
Early transient erythema	2	1.7	0.17	Hours
Main erythema	6	5.0	0.50	10 days
Temporary epilation	3	2.5	0.25	3 weeks
Permanent epilation	7	5.8	0.58	3 weeks
Dry desquamation	10	8.3	0.83	4 weeks
Moist desquamation	15	12.5	1.25	4 weeks
Secondary ulceration	20	16.7	1.67	>6 weeks
Late erythema	15	12.5	1.25	6–10 weeks
Dermal necrosis	18	15.0	1.50	>10 weeks
Dermal atrophy	11	9.2	0.92	>14 weeks
Invasive fibrosis	10	8.3	0.83	–
Telangiectasis	12	10.0	1.00	>52 weeks

* Time required to deliver the typical threshold dose at the specified dose rate.
† Time after single irradiation to observation of effect.

increased to compensate for degraded performance can also result in unnecessarily high absorbed dose and consequent injury from very long exposure times. The timescales for skin injury following fluoroscopy and the threshold skin entrance doses are shown in Table 3.3 (Wagner et al, 1994).

The degree of skin response to radiation varies for different body sites. Kalz (1941) found that skin sensitivity for acute reactions is as follows (in decreasing order): anterior aspect of the neck, antecubital, and popliteal spaces; flexor surfaces of the extremities, chest and abdomen; the face; the back and extensor surfaces of the extremities; the nape of the neck; the scalp; the palms and soles. Hair follicles of the scalp appeared to be more radiosensitive than those in other parts of the body (Trott and Kummermehr, 1991).

Skin sensitivity to radiation can be increased by various chemotherapeutic agents, such as actinomycin D, adriamycin, bleomycin, 5-fluorouracil and methotrexate (Trott and Kummermehr, 1991; Phillips, 1994; Mettler and Upton, 1995).

TABLE 3.3 Threshold skin entrance doses for various skin injuries

Effect	Dose (Gy)	Time to onset of effect
Early transient erythema	2	Hours
Main erythema	6	10 days
Temporary epilation	3	3 weeks
Permanent epilation	7	3 weeks
Dry desquamation	14	4 weeks
Moist desquamation	18	4 weeks
Secondary ulceration	24	>6 weeks
Late erythema	15	8–10 weeks
Ischemic dermal necrosis	18	>10 weeks
Dermal atrophy (1st phase)	10	>12 weeks
Dermal atrophy (2nd phase)	10	>1 year
Induration (invasive fibrosis)	10	–
Telangiectasia	10	>1 year
Late dermal necrosis	>12?	>1 year
Skin cancer	–	>5 years

3.2.3 Diagnosis of radiation-induced skin injury

Some patients who have undergone interventional radiological procedures do not seek attention from their physician for radiation-induced changes. For example, skin lesions can be on the back and not directly visible to the patient. Moreover, many patients have limited mobility and may be less likely to notice skin changes. When lesions are minor, they may go unnoticed. In some cases skin lesions do not cause any pain.

In most cases, when skin injury is noticed, a patient seeks advice from a different physician from the one who performed the fluoroscopic procedure. Usually, they present at some stage to a dermatologist but may not provide a history of prior fluoroscopy because they assume that it is irrelevant for the complaint or have forgotten about it. In many cases, an initial diagnosis of a fixed drug eruption, morphea (circumscribed cutaneous scleroderma), contact dermatitis, viral or bacterial infection, is made. Consequently, the correct diagnosis is delayed.

3.2.4 General principles on the use of interventional radiology

The principles below on the use of interventional radiology are adapted from those issued by the FDA (1994).

- a **Operating procedures** Standard operating procedures and clinical protocols should be established for each specific type of procedure performed. The protocols should address all aspects of the procedures, such as patient selection, the usual technique used, and actions in response to complications and consideration of limits on fluoroscopy exposure time. It is important to include all fluoroscopic system modes of operation used, including image recording, and to strive for clinically adequate images with the minimum fluoroscopic exposure. The credentials and training for physicians performing fluoroscopy should be assured. The radiation beam should be collimated appropriately and the exposure duration should be minimised. Finally, protocols should be communicated and enforced appropriately.
- b **Monitoring of radiation dose rates** All operators should be trained appropriately and should understand how the system works and the implications for radiation exposure from each mode of operation. The radiation output should be calibrated and documented and information should be recorded permitting estimation of the absorbed dose to the skin.
- c **Dissemination of information** Physicians performing fluoroscopic procedures should be educated in the associated risks and on methods of minimising them. Patients should be counselled regarding the symptoms and risks of large radiation exposures.
- d **Protocol modification** The protocol should be modified as appropriate, to limit the cumulative absorbed dose to any irradiated area of skin to the minimum necessary for the clinical tasks. The equipment used should incorporate such features as indication of the cumulative fluoroscopic exposure time, indication of the cumulative absorbed dose to the skin, real-time indication of dose rate, 'last image hold' or 'freeze frame' display, and optimum beam filtration.

3.2.5 Discussion

Physicians often have difficulty recognising the cause of fluoroscopy-induced skin injuries because these are rare. Misdiagnoses are frequent and can lead to prolonged and uncertain courses of treatment. Dermatologists and interventionalists should be aware of the potential for skin injuries and recognise the characteristics of such injuries. If a procedure is prolonged or the dose to the skin is known to be high, the patient should be advised to carry out a self-examination about two to three weeks after the procedure to look for skin changes and to contact the interventionalist if any changes are observed. This information is helpful for clinical care and assists in quality control. An extensive check and recheck system excludes errors. Where errors have occurred, they have usually been the result of a calculational error in a small number of fractions within a treatment or due to miscalibration of the machine at the time of installation or subsequent overhaul. Records of non-conformities are regularly reviewed in all radiotherapy and radiology departments; however, with so many protocols and so many personnel, without extreme vigilance there is clearly capacity for errors.

3.3 References

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4 Biological Dosimetry Estimation following Accidental Acute Radiation Exposure

The ability to assess dose rapidly will be essential for patient management and risk evaluation. Such an assessment requires knowledge of an individual's absorbed dose, the extent of exposure (eg whole or partial body) and the nature (ie quality) of the radiation. In the early stages approximate values suffice as physicians initially respond to clinical symptoms. Greater precision is required when it becomes clear that the patient has sustained a high dose and planning begins to prepare for the emergence of later tissue and organ injury sequelae. The extent of physical dosimetric information available in the short term will probably depend on the event. It could range from personal dosimeter badges worn by the patient through to calculations based on any known physical parameters of the source and recollections of distance and time spent in its proximity. Progressing from brief, acute incidents through to dose protraction, accompanied by delayed discovery of the event, calculational approaches become more difficult to apply.

For decisions concerning triage, treatment and patient psychological well-being it is important to have procedures in place to allow some reasonable dosimetry estimation. Below, prior accidents are first reviewed, considering the information that can be learnt from them. Current procedures and information that can provide dosimetry estimations are then discussed, ranging from a consideration of prodromal and haematological signs to cytogenetic analysis. Finally, there is a review of current approaches that have the potential to be useful for dosimetry estimations. One difficulty in estimating individuals' doses following a large-scale accidental exposure is likely to be the limitation of personnel and resources to carry out rapid sampling and analysis. It is important, therefore, to consider the ease of carrying out each method as well as how long after exposure the method remains useful.

4.1 Radiation accidents and incidents

Incidents leading to suspected or actual accidental overexposures of people to ionising radiation occur frequently in industrial, medical or research settings. Many transpire to be false alarms and, fortunately, for those that do prove positive, the vast majority are shown to involve low doses, well below 1 Gy, requiring no medical intervention apart from reassurance on the low likelihood of health consequences. Clinically serious overexposures are therefore rare and in round numbers, worldwide, since 1950 there have been 400 events that led to one or more injured people requiring treatment. Sixty of the events included fatalities due to acute radiation syndrome and the number of deaths since 1950 is 160 (Ricks, 2002). The Chernobyl reactor accident in 1986 (UNSCEAR, 1988) was the single most serious, in terms of early fatalities which numbered 30, but lately there appears to have been no diminution in the rate of radiation-associated deaths, with 34 worldwide since 1990. The overall ratio of serious injuries to fatalities is approximately 10 : 1.

A registry of all known events that have involved significant overexposures to ionising radiation throughout the world since 1945, but excluding the atomic bombings, is maintained at REAC/TS, Oak Ridge TN, USA. Another registry that concentrates on amassing clinical data on casualties has been built up in Ulm and was recently transferred to Würzburg, Germany. It has a searchable database of about 800 case histories. Access to both registries is, of course, limited to *bona fide* professionals.

Radiation accidents can be categorised into several types. ‘Nuclear’ accidents are those that involve a nuclear facility. Examples would be the Chernobyl reactor fire or the criticality accident at the Tokai-mura nuclear plant. Other, non-nuclear, accidents are termed ‘radiological’ and they arise when control of a sealed or unsealed source is lost, causing either an exposure to ionising radiation or a release of radioactivity. Radiological accidents are the more common, and sources involved may be devices such as X-ray sets, sealed gamma-ray emitters, or unsealed radioisotopes such as those used in research laboratories and nuclear medicine departments. People may be overexposed by external irradiation, internal contamination or a combination of both.

Most recorded events have been accidents but in a few instances criminality was involved. The latter includes deliberate irradiations intended to kill or harm certain targeted individuals (see, for example, Collins and Gauden, 1980, and Meara, 2007) and also the theft of sources by people unaware of the dangerous nature of what they were stealing. To date, there have been no mass terrorism attacks involving radiation sources but many accidents, where sources have inadvertently come into the public domain, have paralleled potential terrorism scenarios.

‘Orphan source’ events – for example, where sealed industrial gamma radiography sources become detached from their wind-out cables, are lost and later picked up by members of the public – are regrettably common occurrences. A number of such sources have been taken into homes and over a period of a few weeks have seriously irradiated families (see, for example, IAEA, 1998, and El-Naggar et al, 2002). Others have remained undetected in the workplaces, sometimes causing exposures of many more people. In other situations, sources have been abandoned later to emerge in the public arena (IAEA, 2000a,b). In many respects these events are models for the terrorism scenario of a covertly emplaced sealed source. In the cases of the Goiânia and Ciudad Juarez accidents (IAEA, 1988; Burson and Lushbaugh, 1990), the sources were breached, resulting in considerable environmental contamination and, at Goiânia, ingestion of radioactivity. These events bear similarities with the scenario of contamination from a terrorist ‘white powder’ incident. Similarly, the problems associated with contaminated wounds and embedded radioactive shrapnel, where an explosive device is used to spread radioactivity (‘dirty bomb’), were encountered in a laboratory explosion involving americium-241 (Thompson, 1983).

4.2 Dose estimation using physical dosimetry and clinical features

Radiation dose can be estimated by physical, biological and clinical dosimetry methods. Whole body dosimetry, by reconstructing the event, provides a physical means to estimate dose to the whole body but the machinery is unlikely to be readily available. Physical dosimeters, and measurements on suitable objects that by chance were present in the victims’ pockets, can be used to estimate external dose but this will not be covered here (Göksu, 2003).

Documenting clinical signs and symptoms can, in fact, be very informative and several tables have been compiled to relate such features to dosimetry estimations (see, for example, Table 4.1). Such features can include time to the onset of nausea/vomiting, skin lesions and fatigue. These are relatively crude procedures and, rather than a relationship to dose, most documentations lie on a grading system using degree stages (see, for example, Table 4.1 and Dainiak et al, 2003, and Fliedner, 2006).

TABLE 4.1 Prodromal phase of acute radiation syndrome (ARS): clinical features relating to dose (adapted from IAEA, 1998a)

Symptoms and medical response	ARS degree and the approximate acute whole body dose (Gy)				
	Mild (1–2 Gy)	Moderate (2–4 Gy)	Severe (4–6 Gy)	Very severe (6–8 Gy)	Lethal* (>8 Gy)
Vomiting					
Onset	2 h after exposure or later	1–2 h after exposure	Earlier than 1 h after exposure	Earlier than 30 min after exposure	Earlier than 10 min after exposure
% of incidence	10–50	70–90	100	100	100
Diarrhoea					
Onset	–	–	3–8 h	1–3 h	Within minutes or 1 h
% of incidence	–	–	<10	>10	Almost 100
Headache					
Onset	Slight	Mild	Moderate	Severe	Severe
% of incidence	–	–	50	80	80–90
Consciousness					
Onset	Unaffected	Unaffected	Unaffected	May be altered	Unconsciousness (may last seconds or minutes)
% of incidence	–	–	–	–	100 (at >50 Gy)
Body temperature					
Onset	Normal	Increased	Fever	High fever	High fever
% of incidence	–	10–80	80–100	100	100
Medical response					
	Outpatient observation	Observation in general hospital, treatment in specialised hospital if needed	Treatment in specialised hospital	Treatment in specialised hospital	Palliative treatment (symptomatic only)

* With appropriate supportive therapy individuals may survive for 6 to 12 months with whole body doses as high as 12 Gy.

Medical records of exposed individuals have been compiled into a database and a radiation casualty management software program, the Biological Assessment Tool (BAT), has been used to provide dose estimation based on the compiled data (Sine et al, 2001). This is available from the website of the US Armed Forces Radiobiology Research Institute (www.afrrri.usuhs.mil). BAT can be used to make dosimetry assessment based on clinical features including those described below. The data collected in templates are compared with established dose responses to provide multiparameter dose assessments (see discussion in Waselenko et al, 2004). The AFRRRI is also developing a First-responders Radiological Assessment Triage (FRAT) software program that will provide dosimetry assessment based on signs, symptoms and blood cell counts.

In addition, the International Atomic Energy Agency (www.iaea.org) is developing a software program to facilitate dose estimation based on clinical signs and symptoms. These tools have the potential to be useful prior to chromosomal aberration analysis being available and/or following exposure to higher doses.

4.3 Dose estimation based on lymphocyte depletion kinetics

For dose estimation following exposure to doses high enough to produce a clinical manifestation, a highly useful parameter is an estimation of lymphocyte depletion kinetics (see Table 4.2). The magnitude and rate of lymphocyte depletion is dependent upon dose. For this analysis, a complete differential blood cell count should be obtained at regular intervals after exposure – ideally every 4–8 hours for the first 24 hours and then every 12–24 hours. A simple algorithm based on rate of decline of circulating lymphocytes to estimate whole body dose after acute irradiation has been developed by Goans et al (2001). This method is suitable for doses ranging between 0.5 and 10 Gy. A 50% decrease in absolute lymphocytes within the first 24 hours, followed by a second drop within 48 hours, is normally characteristic of a lethal dose (Dainiak et al, 2003). Similarly, a rapid transient neutrophilia followed by marked neutropaenia is indicative of life-threatening irradiation. However, it is important to remember that patients suffering from burns and trauma may also develop leucopenia as a consequence of these injuries.

TABLE 4.2 Lymphocyte counts in the initial days of acute radiation syndrome (ARS) depending on the acute whole body dose (adapted from IAEA, 1998a)

Degree of ARS	Dose (Gy)	Lymphocyte counts (G/L)*
Preclinical phase	0.1–1.0	1.5–2.5
Mild	1.0–2.0	0.7–1.5
Moderate	2.0–4.0	0.5–0.8
Severe	4.0–6.0	0.3–0.5
Very severe	6.0–8.0	0.1–0.3
Lethal	>8.0	0.0–0.05

*Expressed as 10^9 cells per litre. After 6 days since first exposure.

4.4 Cytogenetic dosimetry

4.4.1 Dicentric assay

Chromosomal aberration dosimetry, using the frequency of dicentric aberrations in metaphases from blood T-lymphocytes, has been employed as a biological dosimeter since the mid-1960s. The dicentric frequency observed in a patient is referred to an *in vitro* dose–response curve prepared by exposing blood specimens to a range of doses from a comparable quality of radiation. Strictly speaking, this method provides an estimate of averaged dose to the peripheral lymphocyte pool, the cells being assayed, but owing to the widespread distribution of these cells this usually approximates quite well to an averaged whole body dose (IAEA, 2001).

A truly whole body exposure produces dicentrics distributed randomly among the examined metaphases, conforming to a Poisson distribution. In accidents where high doses have been received non-uniformly, perhaps as a partial body exposure, this may be reflected by an over-dispersed distribution. In such cases computational methods have been developed to use the non-Poisson distributions to indicate the approximate size of the exposed fraction of the body and its average dose (Sasaki and Miyata, 1968; Dolphin, 1969).

For certain inhomogeneous exposure events cytogenetic dosimetry is ineffective. One obvious situation would be exposure to soft X-rays or to a beta-emitting radionuclide deposited on the skin. The poor penetration of the radiations means that little or no exposure would be received by the peripheral lymphocytes. Another problematic area is the incorporation of many radionuclides. Depending on a nuclide's chemical form and metabolism, this will lead to irradiation of specific organs and tissues. Whilst excess aberrations in lymphocytes may be observed, this does not assist in determining dose to the target tissues of concern. Notable exceptions to this are, however, those nuclides that have a more-or-less uniform distribution within the body, such as caesium-137 that deposits mainly in muscle or tritiated water that becomes incorporated into body water. Cytogenetics is then very effective (Lloyd et al, 1986; IAEA, 1988).

The frequency of aberrations per unit dose induced *in vivo* is the same as that induced *in vitro* with freshly sampled blood maintained at 37°C and there is relatively little donor variability among normal healthy people. This therefore permits the use of a calibration curve previously prepared with blood from a small panel of donors to be used as the basis of the biological dose estimation for an accidental overexposure. The dose–response relationship is highly dependent on radiation quality and therefore a series of calibrations needs to be prepared to cover the types of radiations likely to be encountered in accidents. In practice, most tend to be accidents with gamma rays from sealed sources such as cobalt-60, caesium-137 and iridium-192 used in industrial radiography, medical diagnostic X-rays and radiation beam therapy sources.

For low LET radiations the acute dose–response relationship is best described by the linear-quadratic model, whereas for high LET radiations the response is linear. The quadratic component to the low LET dose response is dependent upon dose rate and reduces with dose protraction. Again, computational methods have been developed to allow for adjusting the calibration when the exposure is received non-acutely, ie over longer than around half an hour up to one day (Lea and Catcheside, 1942). Beyond

one day simple linearity may be assumed. The linear or linear-quadratic response holds over the dose range that encompasses most radiation accidents but, starting at around 5 Gy acute gamma rays, a saturation effect begins to develop and the curves tend to flatten at very high doses (Lloyd and Edwards, 1983). This imposes greater uncertainty on high dose estimates.

Mixed radiation fields may occasionally be encountered, such as in a criticality accident where both gamma rays and fission neutrons are involved. The simplest approach, as used at Tokai-mura, is to express the measured cytogenetic damage as equivalent dose in gray (Gy Eq), ie as being equivalent to a dose from gamma rays only (Hayata et al, 2001). However, computational methods employing Bayesian statistics can be used to isolate the dicentrics attributable to each of the radiations and so derive separate neutron and gamma doses. This has proved very reliable in simulated criticality accidents (Voisin et al, 2004).

The dicentric assay is the most frequently used biological dosimeter and refinements over about 50 years have led to its development into a routine assay. Experience has shown that it is able to relieve anxiety in false alarms and, where exposures have occurred, give credible estimates when compared with other sources of information concerning an accident. Sometimes, however, where physical dosimetry is lacking, and the circumstances are too poorly known to permit calculations, the biological method may be the only means available to quantify an overexposure.

A major advantage of the dicentric assay is its low control frequency, around 1 per 1000 cells in people exposed to normal background radiation (Lloyd et al, 1980). This arises because there are few other clastogens that induce dicentrics in circulating G₀ lymphocytes. It means that the dicentric assay is the method of choice for evaluating low doses, down to around 100 mGy of X-rays or gamma rays, and over the whole of the useful dose range of the assay there is minimal confounding from, for example, previous exposures to chemicals.

A disadvantage of the assay is that the analysis is time consuming. For an accident involving just one or two casualties the dose estimates can be available about 60 hours from receipt of the blood specimen. Fifty hours is required for cell culturing and processing, when of course many samples can be handled concurrently, but the main 'bottleneck' is the need for slide scoring by skilled microscopists. This can be assisted by automated metaphase finding that removes about two-thirds of the labour (Finnon et al, 1986). As there are few experienced specialist laboratories worldwide, the surge capacity to respond to a mass irradiation event is quite limited. Provision for mutual assistance networking is being developed (Miller et al, 2007) and also using the dicentric assay in a rapid response triage mode (Lloyd et al, 2000). This involves a limited number of cells being scored per sample initially to produce an approximate dose estimate that is sufficient to assist physicians in early prioritising and treatment planning. Table 4.3, taken from an ISO standard on triage cytogenetic dosimetry (ISO, 2008), illustrates the dose estimates and their uncertainties obtained by this approach. In some exercises, simulating 150–200 serious casualties, this triage method proved remarkably effective (Lloyd et al, 2000; Miller et al, 2007). The delay before cytogenetics can inform physicians of the dose to a patient may become important in arriving at clinical decisions concerning whether to commence cytokine therapy.

Another disadvantage concerns the persistence of the dicentric in the peripheral lymphocyte pool which is a function of the lymphocyte renewal rate. Fortunately in people with normal haematology this is

relatively slow. Whilst individual variability must exist, a disappearance half-time of about three years is suggested which, for most practical purposes, means that the dicentric assay is reliable (IAEA, 2001). However, following high doses, sufficient to cause a rapid lymphopaenia, the dicentric frequency reduces rapidly and then the time delay between irradiation and blood sampling becomes important. It could lead to an underestimation of dose when applied, for example, to cases with delayed discovery of serious exposures to orphan sources (Sevan'kaev et al, 2002).

TABLE 4.3 Example of doses, with 95% confidence intervals (CI), for gamma irradiation based on dicentric frequencies in 50 metaphases or stopping scoring at 30 dicentrics. With this triage protocol there are 80 possible combinations; not all are shown here

Dicentrics	Cells	Acute exposure (Gy) (95% CI)		Chronic exposure (Gy) (95% CI)	
0	50	0	(0-0.9)	0	(0-3.6)
1	50	0.4	(0-1.2)	1.0	(0-5.5)
2	50	0.7	(0.1-1.4)	2.0	(0.2-7.2)
3	50	0.8	(0.3-1.5)	3.0	(0.6-8.7)
4	50	1.0	(0.4-1.7)	4.0	(1.0-10.2)
5	50	1.1	(0.6-1.8)	5.0	(1.6-11.6)
10	50	1.7	(1.1-2.3)	10	(4.8-18)
15	50	2.1	(1.5-2.7)	15	(8.4-25)
20	50	2.4	(1.9-3.0)	20	(12-31)
25	50	2.7	(2.2-3.3)	25	(16-37)
30	50	3.0	(2.4-3.6)	30	(20-43)
30	45	3.2	(2.6-3.8)	33	(22-48)
30	40	3.4	(2.7-4.1)	37	(25-53)
30	35	3.6	(2.9-4.4)	43	(29-61)
30	30	3.9	(3.2-4.7)	50	(34-71)
30	25	4.3	(3.5-5.2)	60	(40-85)
30	20	4.8	(3.9-5.8)	75	(51-110)
30	15	5.6	(4.6-6.7)	100	(67-140)
30	10	6.9	(5.8-8.3)	150	(100-210)
30	5	10	(8.0-12)	300	(200-430)

Yet another disadvantage of the dicentric assay, which is of particular concern for high doses, is that irradiated cells may be impeded in completing the cell cycle and so fail to arrive at metaphase for analysis. Delays may arise at cycle checkpoints and interphase death by apoptotic processes may also occur. When a partial body exposure has occurred, the irradiated fraction of lymphocytes will be selectively disadvantaged in culture and so skew the dicentric picture (Lloyd et al, 1973).

The three main problems outlined above, time-consuming skilled analysis, persistence of signal and interphase death/delay, have long been recognised. Nevertheless the dicentric assay is still regarded as the 'gold standard' for biological dosimetry. Fortunately some methods, discussed below, are available to help mitigate these disadvantages.

4.4.2 Micronucleus method

This has the potential for reducing the time spent at the microscope because the images are simpler than for metaphases. Damage may be scored more rapidly and by less skilled staff. Micronuclei are formed when aberrant chromosomes, acentric fragments or sometimes whole chromosomes fail to segregate properly at mitosis and locate in the cytoplasm instead of passing into the daughter nuclei. They stain positive for DNA and so appear as small, rounded objects alongside the nucleus. The major breakthrough in this assay was cytokinesis blocking, so that following the formation of the two daughter nuclei it became possible to stop the cytoplasm dividing (Fenech and Morley, 1985), which leads to the formation of a binucleate cell. By confining the counting of micronuclei to binucleate cells it could be guaranteed that scoring was confined to cells that had passed through one *in vitro* cell cycle.

Just as with dicentrics, calibration curves for micronuclei may be prepared by *in vitro* exposure of blood samples with known doses of defined qualities of radiations. The low dose portions of the curves are subject to more uncertainty because micronuclei are also produced by other clastogens and so there is a higher and more varied background which limits discrimination of low doses. At high doses where several aberrations are induced in a cell, a process of coalescence may occur so that fewer micronuclei are produced, thereby flattening the curve (Littlefield et al, 1989).

In order to make binucleate preparations for microscopic analysis the cells need 72 hours in culture, whereas by contrast the dicentric assay requires only 48 hours. However, once slides are available the data gathering is much faster, thereby enabling a faster throughput of cases in a mass irradiation incident. The cut-off point where in a multiple casualty event the micronucleus assay might be used in preference to the dicentric is debatable. The availability of slides 24 hours earlier for dicentrics means that with this method dose reports can flow sooner, especially if the assay is used in the triage mode. Another consideration is that in the post-emergency phase a major event will be followed up by possibly years of scientific studies such as epidemiology on larger numbers of less seriously irradiated subjects. Then the availability of archived cultured cells and slides prepared for the dicentric assay would be more informative for estimating individual low doses.

4.4.3 FISH method

Fluorescence *in situ* hybridisation (FISH) or 'chromosome painting' was developed as a retrospective biological dosimeter to circumvent the limited persistence of the dicentric in the lymphocyte pool. By selectively highlighting chromosome pairs in different colours, it proved possible to detect stable translocations between chromosomes far more readily than the earlier banding methods (Pinkel et al, 1986). In contrast to the unstable dicentric, translocations will generally be transmitted successfully to daughter cells. Thus as lymphocyte renewal occurs, translocations induced in stem cells will eventually appear in the functional lymphocytes. Sampled many years later these persisting translocations provide a retrospective estimate of stem cell dose and by implication whole body dose (Edwards et al, 2005). Its value in this respect has been demonstrated but initially little use was imagined for FISH in an immediate emergency response to a serious radiation event. However, its value has been shown on several occasions when approximately a month elapsed between irradiation and discovery during which time the patients became severely leucopaenic (IAEA, 1998b, 2000a; Sevan'kaev et al, 2002). Conventional dicentric and FISH analyses made on the same blood samples showed that after such delays the dicentric analysis tended to underestimate the doses by about 20–25%.

4.4.4 Prematurely condensed chromosome methods

Normally chromosomes can only be discerned as discrete objects when they condense at mitosis, otherwise the chromatin appears diffuse. It is, however, possible to cause interphase chromatin to condense into discrete chromosomes and so permit aberrations to be seen. One technique for prematurely condensing the chromosomes is to fuse human G₀ lymphocytes with cultured cells, such as Chinese hamster ovary (CHO) cells, in mitosis (Johnson and Rao, 1970). The condensed human chromosomes can then be easily distinguished from the rodent chromosomes because the latter have two chromatids whilst the human are single stranded. Prematurely condensed chromosome (PCC) preparations by this method can be ready for microscopic analysis within two hours or so of receipt of the blood specimen and the preferred analysis is to count the number of objects in spreads of Giemsa-stained human chromosomes. Any number in excess of 46 in a cell represents induced acentric fragments. It is also possible to carry out FISH analysis on the chromosomes with a pancentromeric probe to observe dicentrics (Pantelias and Maillie, 1984).

To date, no radiation accident cases have been analysed by this method, but in simulations it has highlighted two potential advantages. First, by removing the need for culture to metaphase, a dose estimate may be made more quickly. Second, following a partial body exposure, the proportion of aberrant cells seen can give a direct indication of both the proportion of the body exposed and the mean dose to that volume, because selective losses of the irradiated fraction by death or delay during the *in vitro* cell cycle are avoided (Darroudi et al, 1998).

The inevitable low mitotic indices, possibly reduced to zero, after exceptionally high doses impose a practical limit on using the conventional dicentric in metaphase assay. PCC methods that use chemicals, okadaic acid or calyculin A to induce condensation, rather than mitotic CHO cells, have also been developed (Durante et al, 1998; Kanda et al, 1999). These still require the lymphocytes to be held in

culture and so rapid dose estimation is not possible. The high doses induce so many aberrations that it is impossible to count PCC dicentrics or fragments reliably. However, ring aberrations are induced at a lower, more manageable frequency and their dose response, investigated up to 20 Gy, is linear. PCC rings, visualised by the okadaic acid method, were used successfully on the three victims of the Tokai-mura criticality accident and gave dose estimates of about 20, 8 and 2 Gy Eq, in very good agreement with those from dicentrics and sodium-24 in blood (Hayata et al, 2001).

4.5 Developing methods based on the molecular biology of radiation damage

4.5.1 γ H2AX foci analysis

One of the earliest responses to ionising radiation is activation of a cellular DNA damage response signalling process. Central to this process is a kinase called ataxia telangiectasia mutated (ATM) (Shiloh, 2003). ATM rapidly becomes phosphorylated itself, probably via autophosphorylation, and then phosphorylates a range of protein substrates (Bakkenist and Kastan, 2003). A key substrate is H2AX, a variant form of a protein, H2A, which coats the DNA (Paull et al, 2000). Ionising radiation induces double strand breaks in DNA, which represent the major lethal lesion, and H2AX in the vicinity of the double strand break becomes phosphorylated. The phosphorylated H2AX spreads some distance from the double strand break (Rogakou et al, 1999). Antibodies specific for this phosphorylated form of H2AX have been developed. Following fixing and staining of cells with fluorescent antibodies to phosphorylated H2AX, individual fluorescent foci, termed γ H2AX foci, can be observed. At doses up to around 5 Gy, there is a good correlation between the number of γ H2AX foci and double strand breaks induced in the G₀/G₁ phase cells (above this individual foci cannot be identified). Furthermore, the rate of loss of γ H2AX foci correlates with the rate of double strand break repair estimated by other procedures (Rothkamm and Lobrich, 2003).

H2AX phosphorylation can also arise from other forms of DNA damage as well as during replication. However, the background levels are normally low in cells and the marked formation of foci is characteristic of exposure to ionising radiation. This is a highly sensitive method that is being developed to identify exposure to radiation and has also the potential to identify individuals with impaired double strand break repair, and who are hence likely to respond dramatically to radiation exposure.

The rate of loss of γ H2AX foci also depends upon the quality of radiation, with higher LET radiation having a slower rate of loss of foci compared to low LET radiation (Riballo et al, 2004). Thus, the rate of loss of foci can be informative in assessing the quality of the radiation. Following exposure to higher doses, the early induction rate of foci may not be quantifiable but foci remaining at later times could provide an estimation of dose. For lower dose exposures, the method is likely to require analysis within 24–48 hours of exposure, before the completion of double strand break repair. Until recently, this procedure was carried out primarily on cells (mainly fibroblasts) exposed in culture. However, a recent analysis examined γ H2AX foci in lymphocytes derived from patients subjected to computed tomography (CT) examinations (Lobrich et al, 2005). The number of γ H2AX foci induced was linearly dependent upon the dose-length

product, which represented the local dose delivered and the length of the body exposed. Analysis of lymphocytes sampled at times after exposure showed loss of the foci that correlated with repair rates estimated from *in vitro* exposure. This, therefore, strongly suggests that this is a highly sensitive method to monitor induction and repair of double strand breaks *in vivo*. This analysis was carried out on lymphocytes but ongoing studies with mice indicate that the procedure is applicable to the analysis of additional tissues (P Jeggo and D C Lloyd, personal communication). Currently, γ H2AX foci are counted manually by microscopic analysis. However, studies are under way to derive a quantification for this procedure suitable for high throughput analysis (Kataoka et al, 2006; Nakamura et al, 2006). This might be difficult to achieve following exposure to low doses but should be possible for high dose estimations.

4.5.2 Dose estimation based on the identification of a stable biomarker for radiation exposure

The development of FISH techniques has been discussed above as an application based on currently available data. Here, further potential developments for this technique are discussed. Studies using multifluor FISH (mFISH), which allows individual chromosomes to be identified by colour, have highlighted the fact that radiation induces highly complex aberrations and that the majority of cells with such aberrations fail to proliferate due to their complexity (Anderson et al, 2002, 2003, 2006). This is particularly true after exposure to high LET radiation. As a consequence, there is a rapid decrease in aberration frequency with cell division (Anderson et al, 2000, 2003). Thus, the biologically important aberration is one that is stable and transmissible. It has become clear that, particularly after high LET exposure, formation of stable, transmissible aberrations are relatively rare events but have the potential to provide an important biomarker for radiation exposure (Anderson et al, 2000, 2003; Hande et al, 2003; Mitchell et al, 2004). Moreover, it has also been argued that stable, transmissible aberrations could provide a useful tool for dosimetry estimation, capable of use at prolonged times post-treatment. The rationale is that although stable, transmissible aberrations may arise rarely, they should arise in a manner dependent upon dose and radiation quality. The existence of such stable, complex translocations was observed in workers at the Mayak weapons facility in Russia many years after exposure (Hande et al, 2003), following exposure to plutonium but not to gamma radiation. Moreover, the technique has been utilised to estimate dosimetry for lifetime exposure (see the review by Edwards et al, 2005). Studies are currently under way to determine whether the formation of such stable, transmissible aberrations can be used to estimate dose after chronic exposure. If this proves to be the case, it could provide a useful method for dosimetry estimation at longer times post-exposure. It may also be able to provide information useful for determining the quality of the radiation.

4.5.3 Candidate protein biological dosimeters

A recent literature review of candidate protein biomarkers suitable for individual radiobiological dosimetry (Marchetti et al, 2006) listed 300 publications reporting protein effects in mammalian systems following *in vivo* or *in vitro* radiation exposure, with 173 human radiosensitive proteins being identified. Of these, 47 proteins were responsive at doses below 1 Gy, with 6 being responsive below 0.1 Gy. Many

of the changes observed were phosphorylation changes detectable by phosphorylation-specific antibodies. Phosphorylated H2AX, the protein discussed in Section 4.5.1, was amongst these. Additional candidates were ataxia telangiectasia mutated (ATM), cyclin-dependent kinase inhibitor 1A (CDKN1A) and p53. One suggestion for the utilisation of these is that each one might have different dose and time optima to allow a distinction between dose exposure. The use of phosphorylation-specific antibodies, in particular, would have the possibility to be automated and could potentially provide an informative assay.

4.5.4 Genomic profiling of circulating peripheral blood lymphocytes

One of the most important advances of potential use for dosimetry estimations is the procedure of genomic profiling using microarrays embedded on chips. This procedure monitors the gene expression profile of cells. It is a highly sensitive technique that can detect two- to three-fold changes in gene expression between samples. A number of genes whose expression changes following radiation exposure have been identified and specific chips that contain only those genes may be produced, thereby enabling their altered activity to be monitored. Work to date suggests that this technique has potential applicability for dosimetry estimations (Amundson et al, 2001a,b, 2003, 2004; Amundson and Fornace, 2003). Moreover, it can be used for different cells or tissues, although circulating peripheral blood lymphocytes would represent a convenient source of material. To date, gene expression studies following radiation exposure have been carried out following irradiation of cells *in vitro* and *in vivo*, and radiation-specific profiles have been identified (Amundson and Fornace, 2003). Linear dose responses for the induction of several genes have been observed down to doses as low as 0.02 Gy (Amundson and Fornace, 2003). Whilst this technology looks promising, obstacles still need to be overcome. It is not clear, for example, how long the specific genes remain elevated and thus how rapidly sampling has to be taken. Although the procedure is capable of high throughput, it remains expensive and currently good quality mRNA has to be prepared from each blood sample. This technique, however, in addition to being useful for dosimetry estimations, also has the potential to identify people who might respond poorly to radiation exposure.

4.5.5 Proteomic profiling

The aim of this procedure is to exploit current advances in the ability to monitor changes in protein expression to identify a biomarker of radiation exposure. For dosimetry purposes, it would then be necessary to quantify the protein expression changes and relate them to dose or to establish a dose-dependent panel of such changes. A number of techniques are available to examine protein profiles including high resolution surface-enhanced laser desorption/ionisation time-of-flight (SELDI-TOF) mass spectrometry. One recent study aimed at investigating this technique to identify a biomarker for radiation exposure used SELDI-TOF to generate high throughput proteomic profiles of unfractionated serum samples using a specialised chip (Menard et al, 2006). The utility of the approach was tested using cancer patients before and during radiotherapy. The exposed population could be distinguished from the unexposed population with high sensitivity and specificity. Additionally, high from low dose-volume levels of exposure could be distinguished. From the analysis 23 protein fragments/peptides were uniquely

detected in the exposed group. This demonstrated that the profile of proteins in serum changes following radiation exposure in a manner that is probably dose dependent. However, although this approach has potential, it requires considerable further development and a defined dose–response relationship remains to be determined. It is possible, however, that the development of specific chips will enhance the sensitivity of the technique. Moreover, the procedure, at least in the foreseeable future, is likely to be highly expensive, although with further development it could be capable of high throughput.

4.6 Discussion

To date most radiation accidents have resulted in just one or a few people being irradiated. However, the potential for large-scale accidents or incidents is ever-present. Rapid assessment of absorbed doses is crucial to the triage procedures following large-scale radiological events. For most scenarios it is likely that the majority of irradiated people will not require active medical management but even so dose estimation is valuable for reassurance and counselling. With highly irradiated patients, where clinicians treat according to presenting and developing symptoms, it has long been acknowledged that dose information is very helpful.

Among the biological parameters, the early prodromal responses are informative but subject to wide individual variation. More quantitative estimations can be obtained from changes in differential white cell counts, which of course can be done routinely in any hospital. However, if required *en masse*, local resources would soon be swamped. The same applies to the other biological dosimeters that have been reviewed here. They require more specialist laboratory facilities and skills for which nationally there are just one or two centres. A summary of the advantages and limitations of existing and developing methods for biological dosimetry is given in Table 4.4. The cytogenetic endpoints are the most readily deployable, particularly the dicentric assay, as it is already routinely used for small-scale events. The γ H2AX assay looks promising in that it can be deployed promptly and consideration is being given (K Rothkamm, personal communication) to automating the assay so that it could be carried out by relatively unskilled staff in a receiving hospital environment with results available in an hour. Because of the transient nature of the signal, its applicability is limited to fairly rapidly identified events rather than covert or delayed discovery exposures. The use of protein biological dosimeters also has the potential to be a sensitive and suitable method for high throughput. It is imperative that further research is available to optimise these technologies for sensitivity and high throughput. The other assays discussed, genomic and proteomic profiling, can be summarised as being in the research stage of development. Their potential has been recognised and their applicability still needs evaluating.

Given that there is a need to improve medical preparedness for large radiological events in the UK, where, in the context of biological dosimetry, might extra resources be directed? Early protein changes following radiation exposure have been identified as discussed and have the possibility to provide sensitive assays. However, these changes only persist for short times post-irradiation and thus it is essential that facilities are available for high throughput. Research is required to optimise the use of these procedures. Transcriptional profiling is also an emerging technology that has the potential to be useful. However, this is currently expensive to carry out on a large scale. Proteomic profiling still remains at a

more developmental stage, although the use of specific chips with the candidate proteins identified has potential.

In the shorter term there are several issues worth highlighting. The first is routine haematology, where there is an interesting nanotechnology development under way in the USA. The concept of 'a-lab-on-a-chip' has been applied to making differential blood cell counts within five minutes using a single-use

TABLE 4.4 Summary of the advantages and disadvantages of existing and developing techniques for assessment of radiation exposure levels

Existing techniques	Advantages	Disadvantages
Dicentric assay	Low background 'noise' Well calibrated Well researched >40 years experience of deployment Tested in triage mode	Limited application to internal contamination Saturates at very high doses Technically demanding
Micronucleus assay	Well calibrated Technically easier and faster throughput than the dicentric assay	Limited persistence of the signal Background precludes low dose discrimination Saturates at high doses
FISH method	Well calibrated Persisting signal	Expensive reagents Technically demanding
PCC method	Avoids differential cell losses in partial body exposure Results can be obtained quickly Can detect exposure to high doses	Rarely used Requires further calibration
Developing methods	Advantages	Disadvantages
γ H2AX analysis	Potentially highly useful Can detect radiosensitive individuals Could provide insight into the quality of radiation	Probably requires analysis 1–2 days post-irradiation Time consuming although applicable for automation
Analysis of stable biomarkers	Could be used for analysis of long times post-irradiation Could provide insight into radiation quality	Time consuming Limited capacity for automation
Candidate protein biological dosimeters	Potentially suitable candidate proteins exist	Probably requires analysis 1–2 days post-irradiation
Genomic profiling	Potentially highly sensitive Potentially high throughput	Requires considerable further development Currently expensive technology
Proteomic profiling	Developing technology	Currently insufficiently sensitive, time consuming and expensive

disposable chip that fits into a handheld computer. This system could be taken into the field and of course has potential applications well beyond radiation emergencies. At present the system has passed its laboratory demonstration stage and has been licensed for production, and commercial prototypes are being constructed. This is a development well worth watching.

For cytogenetic dosimetry the emphasis is on improving surge capacity, although it is appreciated that there are practical limitations. Being able to improve to a point where several hundred specimens can be accommodated is feasible, for several thousands it is not. Laboratory networking is one way, and there is scope for mutual aid agreements to be expanded across Europe. The nucleus of such a network exists between the UK, France and Germany. Another direction is to form a network within a country and this has been set up in France, Canada, Japan and one state (Connecticut) in the USA. These networks comprise arrangements whereby a lead specialist biological dosimetry laboratory can mobilise extra resources in clinical cytogenetics units. They require some running costs in maintaining training and quality assurance of staff to perform the dicentric assay that is outside their normal routine work.

When assessing dose to an individual, data from all available sources are amalgamated. These may be obtained by physical and biological methods but it is only the latter that have been considered in this chapter. Nevertheless it is important to acknowledge that even if a casualty had not been wearing a traditional monitoring badge, there are a number of physical measurement options still available. Electron spin resonance (ESR) or optically stimulated luminescence (OSL) can be applied to tooth enamel or finger nails and also to a wide variety of objects that people may have about them at the time of the incident. These are as diverse as matchsticks, coins, buttons, sugar-coated pills, and silicon chips in mobile phones. In the USA consideration is being given to deliberately incorporating tiny crystals of carbon-doped aluminium oxide into the manufacture of credit cards, driving licenses and the like. Thus every citizen, probably unknowingly, would be carrying a highly sensitive and reproducible OSL dosimeter on a card which already has their machine-readable personal identification information. ESR in particular is routinely available in many countries and OSL is being actively researched. Nowhere in the UK are any of these methods available or being researched and this would appear to be a national shortcoming.

4.7 References

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5 Treatment of the Effects of Exposure to High Doses of Ionising Radiation

Over the years there have been many papers published on the treatment of radiation injury to normal tissues in man, and it is not the purpose in this chapter to attempt to produce a definitive thesis on irradiated tissue treatments. Moreover there have been many reviews of this topic. The most recent is by Jarrett et al (2007) and permission has been obtained to reproduce this article in full in this report. It is reproduced with the kind permission of the authors and publisher as an appendix to this chapter (Appendix A). The discussion here is confined to a summary of its contents and some notes on the similarities and differences between the situation in the UK and the USA.

Jarrett et al reviewed the assessment and management of highly irradiated people. Their paper deals chronologically with exposure and contamination criteria, deterministic and stochastic effects, and then the medical management of radiation injury. Under the last category the review deals with all aspects of medical management, from initial evaluation and decontamination to the management of acute radiation sickness, including the three main radiation syndromes (the haematopoietic, gastrointestinal and cerebrovascular syndromes – the last sometimes called the neurovascular syndrome). Unsurprisingly, there is some emphasis on the management of haematopoietic system damage and general supportive care principles including management of infection. A further section deals with the management of internal contamination from the routes of intake and the countermeasures that may be undertaken to stop further deposition and reduce the absorbed radiation dose and also the effects from chemical toxicity. There is a small section on the management of the cutaneous radiation syndrome but little on multiple organ damage.

The review by Jarrett et al is written in the context of institutional structures in the USA, but this readily translates to the UK. Certainly the American experience of irradiated casualties is more extensive than that in the UK, although thankfully rather limited in recent years. Over the years in the USA there has been a conscious combined civilian (Department of Energy) and military initiative to maintain and improve on the ‘corporate clinical memory’ of handling a variety of serious overexposures. These have ranged from criticality accidents during the early days of the nuclear arms race through to industrial accidents and medical maladministrations of radiation. This initiative has resulted in a continuing small body of very knowledgeable physicians who, from time to time, produce high quality specialist publications (Mettler and Moseley, 1985; Mettler et al, 1990; Gusev et al, 2001; Ricks et al, 2002). These people would form the nucleus of any national medical response to a major radiation event in the USA. By contrast, there would appear to be no such committed ‘college’ in the UK.

As well as reviewing the current treatment strategies, Jarrett et al have quite rightly highlighted the current gaps in the knowledge of radiation treatments and have reproduced a list of a number of priority

research areas as recently identified and published by a working group in the USA (Pellmar et al, 2005). This list mirrors that recently produced by the Committee on Medical Aspects of Radiation in the Environment (COMARE) in a paper to the UK Department of Health. Again permission has been obtained to publish this list of research goals here (see Appendix B). These two lists are remarkably similar. We would like to say here and will repeat in our recommendations chapter that we fully endorse the requirement for further research in the areas outlined in these two lists.

Finally, Jarrett et al briefly reviewed several promising developments which, at that time, appeared to be close to the point where they might be deployed for treating irradiated people. There is one further, newer development that should be added to the list. Mesenchymal stem cells, derived from the marrow of the irradiated person, were used with remarkable success in treating localised, severe burns to skin and underlying tissues. The experience, to date, is with two patients sent to the Percy Hospital, Paris, following serious accidents with sealed gamma sources in Chile in 2006 (Lataillade et al, 2007) and more recently in Dakar (unpublished). In both cases use of the stem cells substantially improved the speed and extent of healing of the lesions. A very recent development in the USA is the imminent commercial availability of donor-derived and culture-expanded mesenchymal stem cells (see <http://osiris.com/ars-defense.php>).

5.1 Principles of mass casualty care

Irradiation and contamination, suspected or otherwise, must not distract from the urgent treatment needs of casualties. Contamination, after removal of outer clothing and shoes, typically will be reduced by 85%. Following resuscitation and urgent surgery, as indicated, manifest illness due to irradiation may be treated (initially, in a haematology unit). Militarily, indications for bone marrow transplantation following radiation accidents are considered limited; early bone marrow resuscitation with growth factors, for many as outpatients, is seen to be the way ahead – certainly for larger numbers of potentially immunocompromised casualties.

Possible contamination of a patient presents no significant risk to emergency staff who should receive appropriate information, instruction and training, although provision for their personal protection must be made. Even so, radioactive contamination – or just the suspicion of contamination – will probably hamper emergency response efforts and delay hospital treatment. The only exception is when small pieces of highly radioactive metal, such as cobalt or iridium, have been dispersed and penetrated under the skin of casualties. Patients ‘peppered’ in this manner may well emit significant radiation and will present problems to surgeons who will need to remove the pieces with long forceps to avoid skin doses to their fingers; deep-lying small pieces will also be problematic and may necessitate amputation of limbs in cases where removal is difficult. Clean and dirty treatment areas and access and egress should be segregated, with control of waste and arrangements for monitoring and decontamination of hospital areas, ambulances and associated staff.

Internal contamination should not need to be a major consideration in most cases, especially if sensible precautions (interventions such as sheltering) are implemented where indicated. However, many people, if not most, will demand/require subsequent (reassurance) monitoring and assessment; conceivably, depending upon the circumstances, some people will require decorporation of radioisotope(s). The

management of internal contamination – where indicated in casualties – is, however, neither straightforward nor as successful as should be desired (Holt, 2007). Rarely, bronchopulmonary lavage (BPL) – for heavy pulmonary burdens of, typically, insoluble heavy metal, eg plutonium oxide, and other insoluble radionuclide compounds – to avert deterministic effects (and arguably in the young to reduce lifelong stochastic risks) will require careful consideration of each case on its merits.

Psychological concerns are bound to result – amongst both victims and responders – and people may, in many cases, respond to the provision of information, explanation and reassurance (PIER).

Planning, training, triage, transport and recording and reporting (of casualties) are fundamental to preparing for and managing any major incident, but require additional consideration of irradiation and contamination of, and spread by, both victims and responders.

Information programmes for both internal (health authority) and public use may well be key to the successful management of any crisis, as will effective media strategies at both national and local levels.

5.2 Potential emerging strategies for treatment of and/or protection from radiation injury

Knowledge is rapidly increasing in the understanding of factors required to regenerate cells or stimulate their division and, perhaps more interestingly, in how to exploit stem cells to ameliorate tissue injury. These strategies have the potential to be exploited to improve the treatment of radiation injury and their optimisation requires ongoing research.

As discussed elsewhere, injury to the haematopoietic system is a major consequence of radiation exposure, which particularly results in reduced neutrophil and platelet numbers. An important emerging strategy for the treatment of radiation injury is the stimulation, maintenance and proliferation of progenitor cells from bone marrow (Herodin and Drouet, 2005; Hosseinimehr, 2007). Haematopoietic growth factors and cytokines are used to stimulate the division and differentiation of haematopoietic stem cells. For cytokines to exert their effect, stem cell populations must not be reduced too dramatically and this strategy is thus only useful for the treatment of patients exposed to intermediate doses (Herodin and Drouet, 2005). Such treatment, however, can be particularly useful to enhance the numbers of granulocytes, lymphocytes and platelets, which can help reduce infection and thrombocytopaenia following radiation exposure. Such treatment is also potentially applicable to other tissues using different cytokines. Interleukin-11 is a multifunctional cytokine, which has been used to ameliorate intestinal radiation injury (Boerma et al, 2007), as well as injury to the haematopoietic system (Hao et al, 2004). There is potential in such approaches and a number of distinct pleiotropic cytokines exist, but further work is required for optimisation (Herodin and Drouet, 2005; Herodin et al, 2005).

A distinct, but related approach involves exploitation of the current advancing knowledge of stem cell biology. This can be particularly useful where local radiation injury may cause reduced function of tissue stem cells and prevent the normal replacement of damaged cells, effectively resulting in loss of homeostasis. The ultimate approach may be the use of multipotent, embryonic stem cells to replace the loss of any stem cell compartment. However, other strategies have also been described. One approach

involves *ex vivo* expansion of residual autologous haematopoietic stem and progenitor cells (Mourcin et al, 2005). An alternative and potentially more useful approach is based on emerging evidence that bone marrow derived stem cells can provide a source of regeneration of damaged tissues by mobilisation. One example where this has been studied is following radiation-induced damage to salivary glands (Lombaert et al, 2006). Strikingly, it has been shown that granulocyte colony-stimulating factor (G-CSF) can enhance the mobilisation of bone marrow cells to damaged salivary glands, where they can enhance tissue repair without differentiation into salivary gland cells. Bone marrow derived cells seem to be particularly good at homing to new sites, particularly when used in combination with growth factors. Clearly, such treatment will not be useful if the radiation injury impacts upon the haematopoietic system, but it is possible that other stem cells may be exploitable in a similar way. In this context, mesenchymal stem cells, which reside in several adult tissues such as bone marrow, adipose tissue, cartilage and skin, show potential (Bertho et al, 2005; Francois et al, 2007; Mousieddine et al, 2007). Under certain physiological and pathological conditions, they migrate to organs in which they do not normally reside by circulating through the bloodstream (Son et al, 2006; Ponte et al, 2007). They can then function in the repair of damaged tissues and therefore have a potential use for regenerative medicine after radiation injury. A recent study showed that mesenchymal cells were mobilised into the blood in response to skeletal muscle injury and further research is required to assess how to optimise mobilisation after radiation injury (Ramirez et al, 2006).

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Appendix A

Medical Treatment of Radiation Injuries – Current US Status

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Review

Medical treatment of radiation injuries—Current US status

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Abstract

A nuclear incident or major release of radioactive materials likely would result in vast numbers of patients, many of whom would require novel therapy. Fortunately, the numbers of radiation victims in the United States (USA) have been limited to date. If a mass-casualty situation occurs, there will be a need to perform rapid, accurate dose estimates and to provide appropriate medications and other treatment to ameliorate radiation injury.

The medical management of radiation injury is complex. Radiation injury may include acute radiation sickness (ARS) from external and/or internal radiation exposure, internal organ damage from incorporated radioactive isotopes, and cutaneous injury. Human and animal data have shown that optimal medical care may nearly double the survivable dose of ionizing radiation. Current treatment strategies for radiation injuries are discussed with concentration on the medical management of the hematopoietic syndrome.

In addition, priority areas for continuing and future research into both acute deterministic injuries and also long-term stochastic sequelae of radiation exposure have been identified. There are several near-term novel therapies that appear to offer excellent prognosis for radiation casualties, and these are also described.

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Keywords: Radiation; Radiation injury; Acute radiation syndrome; Acute radiation sickness; Nuclear incident; Dirty bomb; Nuclear explosion; Radiation exposure; Neutropenia; Bone marrow injury; Treatment of radiation exposure; Disaster management; Biodosimetry; Cytokines; Contamination; Chernobyl; Mass casualty

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1. Introduction

Early work in the Atomic Energy Commission (predecessor of the Department of Energy) with nuclear weapons production occasionally resulted in accidents with very high radiation exposures. Fortunately, the number of radiation victims in the United States has been limited by industrial safety protocols that have provided excellent protection for both radiation workers and the general public. Although there have been numerous cases of medical misadministration in hospitals, few of these have resulted in lethal radiation exposure. Nevertheless, the potential for mass casualties in the USA from a deliberate radiation or nuclear incident is real.

We base our doctrine for treating radiation injuries on worldwide (i) historical data, (ii) animal research, and (iii) human results with medical treatment such as the complex care provided to cancer patients who undergo radiation therapy and radiomimetic chemotherapy. Worldwide accident data are recorded and maintained at the Radiation Emergency Assistance Center and Training Site (REAC/TS) in Oak Ridge, TN, USA.

Based on historical experience, major radiation accidents and incidents generally deliver combined injury (radiation and/or thermal and/or mechanical trauma) to casualties. Exposure to significant doses of radiation delays or suppresses immune and tissue repair system responses, thus worsening the prognosis in patients with other traumatic injuries. Treatment modalities, particularly the timing of surgical interventions, may also be changed. For purposes of simplicity, this paper will focus on radiation injury management alone. Radiation injury may include acute radiation sickness (ARS; also called acute radiation syndrome), the organ-specific effects of external and internal contamination, and cutaneous injury. Treatment of all of these will be described, but we will focus on the medical management of the hematopoietic syndrome which may benefit the most victims.

2. General principles of radiation exposure and injury

2.1. Exposure versus contamination

There is often confusion in the lay public (and even among some medical professionals) regarding the difference between radiation exposure and radioactive contamination. Exposure means that the body has absorbed energy from radioactive materials or other sources of radiation; contamination means these sources are still on, or in the person's body or clothing. Radiation exposure primarily results from penetrating particle or photon radiation from powerful radiation sources located away from the body (external radiation), as well as radiation from contamination by radioactive fragments or particulates located on external surfaces (clothing or body) or internalized within the body (internal radiation contamination). The purpose of decontamination is to reduce further exposure to the casualty as well as limit the spread of radioactive material.

The U.S. Institute of Medicine publication, Potential Radiation Exposure in Military Operations: Protecting the Soldier Before, During, and After, provides specified exposure limits and the associated protective guidance for decision makers managing potential radiation exposure during military operations (Mettler et al., 1999). Potential radiological exposures during deployment may result from the accidental or intentional loss of positive control over industrial, institutional, medical, or military radiation sources. Examples may include damaged or sabotaged nuclear reactors, unmarked or damaged medical or commercial radiation sources, unmarked waste dumps, and intentionally contaminated conventional explosives. Industrial sources tend to contain relatively powerful radionuclides with long half-lives, and potentially are dangerous for that reason. Medical and university sources may have less than optimal security and suffer inappropriate dispositions, notably when facilities are abandoned. Military-specific threats include cesium (Cs), cobalt (Co), iodine (I), uranium (U), plutonium (Pu),

radium (Ra), strontium (Sr), and tritium (H-3) due to their presence in military equipment or their being produced specifically by or sourced from potential weapon systems. Large commercial sterilization irradiators use Cs-137 and Co-60, the latter being more common. Isotopes used for industrial radiography include californium (Cf-252), Cs-137, Co-60, and iridium (Ir-192). Additional isotopes are used in industry and may be stolen, abandoned, inappropriately disposed, or otherwise present a hazard. Historically, the most common causes of internal contamination are accidents, mostly in industrial and institutional settings, including medical misadministration.

2.2. Deterministic versus stochastic radiation effects

Deterministic effects are those signs, symptoms, and disease entities whose severity can be directly related to the absorbed radiation dose. Clinical effects usually are unapparent at exposure levels less than a threshold radiation dose. All radiation-induced signs and symptoms such as lethargy, vomiting, skin erythema, hematopoietic depression, infertility, cataracts, etc., are deterministic and appear in a time-phased manner.

Stochastic effects are based on specific disease incidence over time in a given population. The probability of occurrence of a stochastic effect is believed to depend upon dose but the severity of the specific disease state does not. Stochastic effects, such as certain cancers, may not appear for years after the incident. Current doctrine holds that there is no threshold dose for stochastic effects, but this is controversial and some data suggest that a dose threshold may exist (BEIR VII, 2006).

With reasonable precautions, health-care providers will not receive an irradiation dose from a contaminated patient sufficient to induce deterministic radiation effects. The purpose of radiation precautions for providers is to reduce the probability of occurrence of stochastic effects.

3. Medical management of radiation injury

The focus of this article is on the medical management of the acute phase of the hematopoietic syndrome that is part of the acute radiation syndrome. The reader is referred to several other publications which describe early and late management of radiation injury including the acute radiation syndrome, the cutaneous syndrome, and multiple organ dysfunction syndrome (Fliedner et al., 2001, 2005; Friesecke et al., 2001; Gorin et al., 2006; Gusev et al., 2001; Herodin and Drouet, 2005; Koenig et al., 2005; Meineke and Fliedner, 2005; Ricks et al., 2002; USDHHS, 2006; Waselenko et al., 2004).

3.1. Initial evaluation and decontamination (DECON)

The immediate response to any radiological casualty *always* should be to promptly address any life-threatening conditions and debilitating injuries first. Decontamination is a secondary consideration. With the possible exception of a strong neutron or gamma radiation source (emitting > 1 Gy/h) near, on,

or inside the patient, radioactive contaminants pose no significant immediate threat either to other patients or to medical responders. Normal universal precautions are appropriate. After stabilizing the patient (airway, breathing, and circulation/hemorrhage control), the evaluation then continues. Because there likely will be no early medical signs or symptoms within the first several minutes after radionuclide exposure, it is critical to obtain a patient exposure history to determine what happened and possibly identify the offending radionuclide(s). Initial contamination *evaluation* steps include a rapid exposure history, rapid initial contamination survey using RADIAC meters, and obtaining moistened nasal swabs (individual bilateral specimens) to help estimate the potential lung deposition of radionuclide(s). A buccal (mouth mucosal) swab also is obtained to screen for oral ingestion. Initial *decontamination* steps include the removal of patient's clothing (85% decontamination effectiveness) and quickly washing the patient with soap and water if feasible (AFRRI, 2003). Exposed skin surfaces such as hands, head and neck, and face are the priority areas for a rapid cleansing. Patients who have been exposed only to external irradiation are not contaminated and pose no threat to any person.

3.1.1. Radiation dose versus response category

The predicted dose a victim received helps guide the appropriate course of treatment. A victim's dose may be estimated by a variety of methods. If the victim was wearing a dosimeter, the dosimeter may provide an accurate dose. Health physicists may be able to construct a dose plume from a source of radiation. A victim's signs and symptoms will vary with dose. The biodosimetry assessment tool (BAT), described in Section 3.2.2, offers a computer program that estimates dose based on time to onset of vomiting, and/or change in serial lymphocyte counts. The gold standard for dose determination is chromosome cytogenetics.

It may not be possible to quickly estimate dose. For example, radiation exposure may not be uniform so that doses of radiation to different parts of the body may vary significantly. A method for medical management based on signs and symptoms was developed by Fliedner and colleagues, and is called "METREPOL" (Medical Treatment Protocols for Radiation Accident Victims as a Basis for a Computerised Guidance System.) This system uses "response categories," and does not rely on either physical or biological estimates of radiation dose. Twenty-seven different clinically observable signs and symptoms are used as indicators of effect. Grading codes are translated into a response category that can be used as a basis for decision-making in medical management as the response codes assign patients to different levels of care (Fliedner et al., 2001; Friesecke et al., 2001).

3.2. Management of acute radiation sickness (ARS)

3.2.1. Definition

ARS (also called acute radiation syndrome) can be defined as the signs and symptoms manifested after exposure to high-dose

ionizing radiation. At any medically significant dose of radiation, all organ systems show damage, in varying degrees and in tissue-specific ways. ARS is the consequence of cell renewal, organ system-specific radiation responses including inflammatory reactions and their continuous interplay and system interactions. In general, ARS requires a total body or nearly total body receipt of a dose of ionizing radiation greater than about 1 gray (Gy; 1 Gy equals 100 rad) delivered over a short interval of time. The most rapidly replicative cells are the most acutely sensitive to the effects of radiation, particularly spermatogonia, lympho-hematopoietic elements, and intestinal crypt cells. Consequently, from a physiological standpoint, ARS can be regarded as a combination of syndromes—hematopoietic, gastrointestinal, and neurovascular—that appear in stages and are related directly to the dose of radiation received (Zajtchuk et al., 1989). ARS generally results from exposure to external sources of radiation alone but can occur from internal contamination by highly radioactive isotopes or from exposure to combined external radiation and internal contamination.

3.2.2. Hematopoietic syndrome (≥ 0.7 Gy) (AFRRI, 2003)

Lymphopenia is common and appears within days, before the onset of other cytopenias. A predictable decline in lymphocytes occurs almost immediately after radiation exposure. A 50% decline in absolute lymphocyte count within the first 24 h after exposure, followed by a further, more severe decline within 48 h, characterizes a potentially lethal exposure (Mettler and Upton, 1995; AFRRI, 2003; Waselenko et al., 2004). Lymphocyte depression is maximal at 10–15 days, and may take 3–6 months to recover. Time to nadir is inversely proportional to dose, and depth and duration are proportional to dose; this is true of other peripheral blood elements as well. The BAT provided by the Uniformed Services University Armed Forces Radiobiology Research Institute (AFRRI) in Bethesda, MD, can aid in dose estimation. This tool is available from the AFRRI website (<http://www.afri.usuhs.mil/>). The onset of other cytopenias depends also on cell sensitivity and dose. Granulocyte counts may transiently increase before decreasing in patients with exposure to less than 5 Gy. This transient increase, termed an abortive rise, may indicate a survivable exposure (Waselenko et al., 2004). Granulocytes show a decrease over the first 5–8 days (neutrophils have a short life span of only a few hours); full recovery may take several months. Platelets have a longer life span (around 10 days); depending upon dose, the nadir may occur at 1 week (for higher doses) or not until 2–3 weeks later (Mettler and Upton, 1995). Recovery time also can be prolonged similar to granulocytes; as a rule, however, the time to nadir is later and the relative depth of the nadir less than for granulocytes. Erythrocytes have a longer (120 days) lifetime and are not as severely affected by radiation as the other cell lines; nevertheless, transfusion requirements in patients from Chernobyl and other radiation accidents were higher than expected, owing to hemorrhages from small blood vessels rather than from depletion kinetics. Accidental (vice therapeutic whole body) irradiation is almost always inhomogeneous, and portions of the red bone marrow may be heavily

irradiated while other parts may be relatively spared owing to internal and external shielding and other factors. This complicates dose assessment using depletion kinetics. However, there are special tests, such as the premature chromosome condensation (PCC) assay, that can compensate for inhomogeneity of exposure (Prasanna et al., 1995).

3.2.3. Gastrointestinal syndrome (≥ 6 Gy) (AFRRI, 2003) and multiple organ dysfunction syndrome (Herodin and Drouet, 2005)

Radiation causes loss of intestinal crypts and breakdown of the mucosal barrier that result in abdominal pain, diarrhea, nausea and vomiting, and predisposes patients to infection. Systemic effects may include malabsorption resulting in malnutrition; bowel obstruction due to ileus; dehydration, cardiovascular collapse, and electrolyte derangements from fluid shifts; damage to the intestinal mucosa and microcirculation with subsequent gastrointestinal bleeding; sepsis; and acute renal failure (Waselenko et al., 2004). The blood cell lineage changes described in the hematopoietic syndrome occur in even more marked degree. Depletion of leukocytes increases the incidence of sepsis from bacterial translocation facilitated by the depletion of intestinal epithelial elements. Mural hemorrhages were seen in the autopsy specimens from Chernobyl as well as in animal models exposed to atmospheric nuclear weapon detonations in Nevada (and Semipalatinsk, Kazakh SSR).

The multiple organ dysfunction syndrome has been described as a delayed effect for radiation victims who survived the hematopoietic syndrome and early gastrointestinal syndrome but demised due to multi-organ failure. Flidner has described both multiple organ involvement and multiple organ failure with whole-body radiation exposure (Flidner et al., 2005). For example, acute radiation pneumonitis develops 2–6 months after exposure and is manifested by cough, dyspnea, and respiratory difficulties. Progressive pulmonary fibrosis usually develops even if the patient initially was asymptomatic; it may not be noted until a year after exposure. Respiratory difficulties increase in severity with time and generally are irreversible (Hall, 2006). Nephropathy manifested by arterial hypertension and anemia has occurred in therapeutically irradiated patients. Hepatitis is another possible late-occurring injury. However, pathology in the kidneys and liver manifests itself much later than the lungs, and at dose levels well above those that are currently survivable in patients receiving whole-body radiation exposure.

3.2.4. Neurovascular syndrome (≥ 20 Gy) (AFRRI, 2003)

Within minutes of a very high dose of radiation, individuals may experience disorientation, confusion, prostration, hypotension, loss of balance and seizures. Physical examination may reveal papilledema, ataxia, and reduced deep tendon and corneal reflexes. Within a few hours, watery diarrhea, respiratory distress, fever and cardiovascular collapse can occur. Death has occurred in as little as 2 days (Zajtchuk et al., 1989). Changes seen in this syndrome may include myocardial damage. This syndrome is sometimes called the cerebrovascular syndrome.

At these doses, survival for more than a few days is impossible with current medical treatment.

3.2.5. General supportive care principles

Supportive therapy is of central importance to minimizing the morbidity and mortality of patients with significant whole-body exposure. Initial symptoms such as nausea, vomiting, and diarrhea should be addressed once other injuries have been medically stabilized, appropriate biological dosimetry samples have been obtained, and, if necessary, the patient decontaminated. Treatment of these early manifestations of ARS may range from minimal intervention to the use of parenteral fluids and antiemetic agents including the serotonin receptor antagonists ondansetron (Zofran®) or granisetron (Kytril®). Although treating acute symptoms are important to minimize fluid loss and patient distress, systematic recording of the signs and symptoms are valuable adjuncts to the estimation of the dose involved. Maintenance of adequate nutrition is important to counter the catabolic effects of radiation and allow healing and recovery. If possible, oral feeding is preferred to maintain functioning of the intestinal mucosa and reduce the inherent infection risk of parenteral nutrition. If the patient is not able to tolerate oral or intermittent tube feeding or if fluid loss is profound due to diarrhea, parenteral feeding may be necessary. Supportive care should include appropriate pain medication, sedatives, and hypnotics.

A major cause of death in ARS is sepsis. A clean environment (preferably reverse isolation) with strict hand washing, scrub suit, caps, masks, gowns, and gloves for staff and visitors is imperative. Another major problem is microvascular occlusion and hemorrhage. Frequent red blood cell and platelet transfusions are necessary at higher doses; all transfusion products should be irradiated to 25 Gy prior to transfusion to diminish graft-versus-host disease.

3.2.6. Management of hematopoietic system damage

Although a drop in lymphocytes will occur within a few hours of a significant radiation exposure, other hematological manifestations may not become clinically apparent until after a 1- to 4-week latent period. One can expect the timing of the hematological response to progress from early reduction in lymphocytes, then neutrophils and other white blood cells, and later reduction in platelets, then red blood cells. Therapy should begin as soon as is practical after injury, and long before the foreordained neutropenia. In ideal situations, marrow resuscitative therapy should begin within 24–48 h of irradiation. As a short-term therapy, cytokine therapy with a human granulocyte colony-stimulating factor (G-CSF), filgrastim (Neupogen®), or with a human granulocyte-macrophage colony-stimulating factor (GM-CSF), sargramostim (Leukine®), may be appropriate. Although there is some controversy regarding timing, the U.S. Strategic National Stockpile Radiation Working Group recommends that treatment with CSFs should be initiated as soon as possible in any adult with a whole-body or significant partial-body exposure greater than 3 Gy. The CSF may be stopped after recovery from the nadir, when the absolute neutrophil count

(ANC) reaches a level greater than 1.0×10^9 cells/L. Reinstitution of CSF treatment may be required if the patient has a significant neutrophil decline ($< 0.5 \times 10^9$ cells/L) after discontinuation. In a small-casualty scenario, prolonged therapy with cytokines, blood component transfusion, and even stem-cell transplantation may be appropriate when exposure dose is > 7 Gy or when traumatic injury or burns also are present (Waselenko et al., 2004). The rationale for using CSFs in the radiation setting is derived from three sources: (a) enhancement of neutrophil recovery in cancer patients treated with CSFs, (b) an apparently diminished period of neutropenia in a small number of radiation accident victims receiving CSFs, and (c) improved survival in irradiated canines and non-human primates treated with CSFs. Colony-stimulating factors increase the survival, amplification, and differentiation of granulocyte progenitors. Both GM-CSF and G-CSF activate or prime neutrophils to enhance their function. In the REAC/TS registry, 25 of 28 patients treated with G-CSF and GM-CSF after radiation accidents appeared to have faster neutrophil recovery. In most instances, these persons received both G-CSF and GM-CSF concurrently for significant periods. There was considerable variation in when and how CSFs were used (often weeks after the incident). Some of these patients also received interleukin-3. A significant survival advantage has been demonstrated in irradiated animals treated with CSFs in the first 24 h (Waselenko et al., 2004). Animal research, primarily from the AFRRI, has demonstrated that early use of cytokines is the preferential timing of administration. Pegylated filgrastim (Neulasta®) appears to be effective, and can diminish the requirement for daily injections.

Children under 12 and adults over 60 may be more susceptible to irradiation and have a lower $LD_{50/60}$ (dose level that causes 50% death within 60 days). Therefore, a lower threshold exposure dose (2 Gy) for initiation of CSF therapy is appropriate in such persons and for patients who have major trauma injuries or burns. Because CSFs are a critical resource that must be provided for some weeks, difficult triage decisions may have to be made in mass casualty situations; Table 1 shows guidelines for treatment of radiologic victims (Waselenko et al., 2004).

Epoetin and darbepoetin are medications that act similar to erythropoietin to stimulate red blood cell production. These medications are indicated for treating anemia due to cancer chemotherapy and chronic renal failure; however, there are no data that validate efficacy in stimulating marrow red cell production following combined injury with acute blood loss and irradiation. Response time is prolonged (e.g., 3–6 weeks), and iron supplementation may be required.

Transfusion of packed red blood cells and platelets may be required for patients with severe bone marrow damage, at earlier times and to greater extent than may be anticipated. All cellular products must be leukoreduced and irradiated to 25 Gy to prevent transfusion-associated graft-versus-host disease in the irradiated (immunosuppressed) patient. Distinguishing between transfusion-associated graft-versus-host disease and radiation-induced organ toxicity may be very difficult. Both may include fevers, pancytopenia, skin rash, desquamation, severe diarrhea, and abnormal liver function tests (in particular,

Table 1
Guidelines for treatment of radiologic victims^a

Variable	Proposed dose range for treatment with cytokines (Gy)	Proposed dose range for treatment with antibiotics ^b (Gy)
Small-volume scenario (≤ 100 casualties)		
Healthy person, no other injuries	3–10 ^c	2–10 ^d
Multiple injuries or burns	2–6 ^c	2–6 ^d
Mass-casualty scenario (> 100 casualties)		
Healthy person, no injuries	3–7 ^c	2–7 ^d
Multiple injuries or burns	2–6 ^c	2–6 ^d

Adapted from Waselenko et al. (2004), Table 7.

^aStrategic National Stockpile Radiation Working Group consensus guidance for treatment is based on threshold whole-body or significant partial-body exposure doses. Events due to explosion of a radiological dispersal device (RDD) resulting in ≤ 100 casualties and those due to detonation of an improvised nuclear device resulting in > 100 casualties were considered. The guidelines were intended to supplement (and not substitute for) clinical findings based on examination of the patient.

^bProphylactic antibiotics include gram-negative and gram-positive coverage, acyclovir (if patient is seropositive for herpes simplex virus or has a medical history of this virus), and fluconazole when absolute neutrophil count is $< 0.5 \times 10^9$ cells/L.

^cConsider initiating therapy at lower exposure dose in children and elderly persons. Initiate treatment with granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor in victims who develop an absolute neutrophil count $< 0.5 \times 10^9$ cells/L and are not already receiving colony-stimulating factor.

^dAbsolute neutrophil count $< 0.5 \times 10^9$ cells/L. Antibiotic therapy should be continued until neutrophil recovery has occurred. Follow Infectious Diseases Society of American guidelines for febrile neutropenia if fever develops while the patient is taking prophylactic medication.

hyperbilirubinemia). Leukoreduction lessens febrile non-hemolytic reactions and the immunosuppressive effects of blood transfusion. Leukoreduction also helps protect against platelet alloimmunization and against acquiring cytomegalovirus infections. Consequently, it is highly recommended that blood products should be both irradiated and leukoreduced prior to administration in irradiation casualties (Waselenko et al., 2004).

A small number of radiation accident victims have undergone allogeneic transplantation from a variety of donors in an attempt to overcome radiation-induced bone marrow aplasia. Many reports demonstrate transient engraftment with partial chimerism (foreign cells from the donor), with nearly all patients experiencing autologous reconstitution of hematopoiesis. However, despite this transient engraftment, outcomes have been poor. In a 1997 review of the allogeneic transplant experience in 29 patients who developed bone marrow failure from previous radiation accidents, all patients with burns died and only three of the 29 lived beyond 1 year (Densow et al., 1997). It is unclear whether the transplants affected survival (Waselenko et al., 2004; Densow et al., 1997). Similar results were observed in the 1999 radiation accident in Tokaimura, Japan, where two of the three victims were referred for allogeneic transplantation. Both patients demonstrated transient evidence of donor-cell engraftment followed by complete autologous hematopoietic recovery before eventually dying of radiation injuries to another organ system or infection (Waselenko et al., 2004; Densow et al., 1997). At Chernobyl, all six patients receiving fetal liver transplants died, and 11 of the 13 who received bone marrow transplantation died. The two survivors regenerated their own marrow, as no donor tissue was found soon after the transplant. It was felt that two or three of the 11 deaths may have been due to graft-versus-host disease. Accordingly, there is controversy regarding the utility of transplantations at all in these scenarios. A transplant may be considered for persons receiving 7–10 Gy and no other significant injury.

Individuals with a granulocyte count exceeding 0.5×10^9 cells/L and a platelet count of more than 100×10^9 cells/L at 6 days after exposure should not have transplantation. In the unusual circumstance that a syngeneic donor may be available or previously harvested autologous marrow is available, a stem-cell infusion may be considered in patients with exposures exceeding 4 Gy (Waselenko et al., 2004).

3.2.7. Management of infection

Susceptibility to infection may result from a breach in the skin or mucosal barriers and immune suppression due to a decline in lymphohematopoietic elements. Several studies have shown that antibiotics reduce mortality rates in irradiated dogs in the LD_{50/30} range. A major factor for a successful outcome is the necessity to control infection during the critical neutropenic phase. In non-neutropenic patients, antibiotic therapy should be directed toward the foci of infection and the most likely pathogens. Fluoroquinolones have been used widely for prophylaxis of neutropenic patients. Patients who experience significant neutropenia with an ANC less than 0.5×10^9 cells/L should receive broad-spectrum prophylactic antimicrobial agents during the neutropenic period. Prophylaxis should include a fluoroquinolone with streptococcal coverage or a fluoroquinolone without streptococcal coverage plus penicillin or amoxicillin, antiviral drugs (acyclovir or one of its congeners), and antifungal agents such as fluconazole.

Antimicrobial agents should be continued until they clearly are not needed or not effective (for example, the neutrophil count recovers above 0.5×10^9 cells/L or the victim continues to have fevers; in the latter case, the antibiotic should be changed). Focal infections that develop during the neutropenic period require a full course of antimicrobial therapy. It should be continued until the ANC has recovered. In patients who experience fever while receiving a fluoroquinolone, it should be withdrawn and therapy should be directed at gram-negative

bacteria (in particular, *Pseudomonas aeruginosa*), because infections of this type may rapidly become fatal. Therapy for patients with neutropenia and fever should be guided by the recommendations of the Infectious Diseases Society of America (Hughes et al., 2002). Use of additional antibiotics is based on treatment of suspected foci (e.g., anaerobic cocci and bacilli that may occur in patients with abdominal trauma, or infection with gram-positive bacteria such as *Staphylococcus* and *Streptococcus* species in addition to significant burns). Altering the anaerobic gut flora of irradiated patients may worsen outcomes. Therefore, gut prophylaxis should not be administered empirically unless it is clinically indicated, as for patients with an abdominal wound. Treatment of anaerobic infections such as *Clostridium difficile* enterocolitis (CDE) would be appropriate and necessary (Waselenko et al., 2004).

Studies in irradiated mice demonstrated that gut flora is altered dramatically soon after acute, high-dose exposure. The total mass of aerobes and anaerobes is reduced by several orders of magnitude, while *Enterobacteriaceae* increase at the expense of vital anaerobic species. In addition to breaks in the integrity of the gut wall, a dose-dependent reduction in the number of stem cells in intestinal crypts occurs in the first few days after radiation. Fatal bacteremia may result from bacterial outgrowth and translocation across damaged walls and interstitium of these organisms to the bloodstream. The use of quinolones was effective in controlling systemic endogenous gram-negative infections after radiation. Supplementation with penicillin prevented treatment failures due to *Streptococci* infection, and also in patients with cancer who experienced treatment-related neutropenia. Quinolones also were effective in preventing endogenous infections with *Klebsiella* and *Pseudomonas* species. Studies in mice also have demonstrated that probiotics such as *Lactobacillus* or *Bifidobacteria* improve or prolong survival; these compounds were also given to some patients at Chernobyl. Though mortality was not affected, length of survival was prolonged and stool cultures for gram-negatives became negative (Korschunov et al., 1998).

If serologic tests for herpes simplex viruses HSV-1 or HSV-2 are known to be positive, acyclovir or a similar medication should be administered prophylactically. Patients with positive serologic results are at high risk for reactivation of HSV infection during intense immunosuppression and may present a clinical scenario that mimics radiation stomatitis. It has been shown that patients who received immunosuppressive therapies such as bone marrow transplantation had a high incidence of reactivation. If serologic results are not known, it would be reasonable to offer HSV prophylaxis based on a history of oral or genital herpes infection. Individuals not previously tested or prophylaxed who experience severe mucositis should be assessed for possible reactivation of HSV.

Oral fluconazole lessens mortality rates and the severity of invasive fungal infections in patients undergoing allogeneic bone marrow transplantation. Fluconazole prophylaxis is ineffective against *Aspergillus*, *Candida krusei*, molds, and other resistant species.

Prolonged immune suppression from radiation may lead to reactivation of CMV (cytomegalovirus) and development of

Pneumocystis jiroveci pneumonia. Extrapolation from the marrow transplant literature indicates that the period of greatest risk for CMV reactivation is within the first 100 days of exposure. If resources allow, the serologic status of CMV should be determined and a sensitive test should be used to assay for reactivation of CMV (that is, antigen assessment or a polymerase chain reaction test) weekly from day 30 post-exposure until day 100 post-exposure in patients with documented previous CMV exposure. Subsequent examination may be necessary based on the clinical scenario because CMV infection may occur later. The absolute CD4 cell count should be assessed 30 days post-exposure for patients who had or have radiation-associated lymphopenia. Patients who have an absolute CD4 cell count less than 0.200×10^9 cells/L are highly susceptible to *Pneumocystis jiroveci* pneumonia. Trimethoprim–sulfamethoxazole should be avoided until the leukocyte count exceeds 3.0×10^9 cells/L or the ANC exceeds 1.5×10^9 cells/L. Alternative therapy includes atovaquone, dapsone, and aerosolized pentamidine. Prophylaxis should continue until the absolute CD4 cell count increases to a level of 0.2×10^9 cells/L or greater. This may not occur for several months.

A patient's immune reconstitution may be abnormal for months after a radiologic incident. In the USA, revaccination should follow guidelines provided by the Centers for Disease Control, the American Society for Bone Marrow Transplantation, and the Infectious Diseases Society of America (CDC/ASBMT/IDSA). Additional consideration should be made for vaccination for Streptococcal pneumonia, *Neisseria meningococcus*, and *Hemophilus influenzae* type B if functional hyposplenism is suspected. Serologies to assess vaccination status should be considered. Prophylactic penicillin V would be appropriate if a serologic response is not achieved. Live vaccines should not be given until at least 24 months after a significant exposure (Waselenko et al., 2006). Even an asymptomatic radiation exposure may modify the immune response.

3.2.8. Other considerations (pregnancy and combined injury)

All hematopoietic cytokines and many antibiotics are U.S. Federal Drug Administration Class C drugs. This means they may be hazardous to a fetus. Radiation exposure also can have deleterious effects on a fetus. Consultation with a health physicist and a maternal–fetal medicine specialist is recommended. Radiation-induced non-cancer effects are not detectable below 50 mGy. The most sensitive period for radiation effects on offspring IQ is 8–15 weeks post-conception. The practical threshold for congenital defects in the human fetus during this time is 100–200 mGy. After 16 weeks this threshold is considered to be 500–700 mGy (CDC, 2006a). Below this level non-cancer effects are not detectable. Of pregnant women at Hiroshima and Nagasaki who demonstrated signs of acute radiation syndrome, 23% had fetal deaths and 20% had neonatal or infant deaths. Pregnant women should receive basically the same supportive care as that provided to non-pregnant women. Antibiotic use in pregnant women requires a review of safe medications in pregnancy. Risks and benefits to the mother and fetus must be explained before therapy is administered.

Detonation of an improvised nuclear device would cause trauma and burn injuries in addition to radiation injury. It is expected that 60–70% of patients after such a detonation would have combined injuries that would complicate significantly the management of patients with the hematopoietic syndrome and significantly lower the LD_{50/60}. Prognosis would be grave in patients with radiation and other injury. Because of impaired wound healing and susceptibility to infection post-significant radiation exposure, any surgical procedures should either be performed within the first 36–48 h or deferred 2 or 3 months, assuming hematopoietic recovery by then (AFRRI, 2003).

3.3. Management of internal contamination

3.3.1. General principles

A radionuclide may be incorporated into the body via inhalation, swallowing, a wound, injection, or other mechanism. The injury produced by the incorporated radionuclide is a function of the amount of radionuclide present, the energy and type of radiation, the radiological half-life, the body's metabolism of the material, and the specific organ or tissue most impacted. The amount of radionuclide in the body is a function of intake, uptake, redistribution, deposition, and elimination. The associated kinetics of absorption and distribution principally are a function of the portal of entry and chemical state, and thus chemical properties of the radionuclide, metabolism and particle size. The *biological half-time*, which differs from the radiological decay half-life, is the time for half the atoms of a substance to be removed from the body. It may range from less than a day to many years, depending on the specific radionuclide.

The *critical organ/tissue* is the location where the radionuclide is deposited or has its principle effect. Both biological half-time and the *target organ* largely are functions of the chemical behavior of the radionuclide. Radioactive isotopes behave chemically like their non-radioactive counterparts. For example, sodium (Na-24) is distributed throughout the whole body, as is cesium (Cs-137), which mimics potassium. Tritium (H-3) as hydrogen gas is exhaled immediately like helium; but tritium as the hydrogen atom in a water molecule is absorbed immediately. The whole-body distribution allows for serum or excretory measurement of the isotope. Radium (Ra-226) and strontium (Sr-90) mimic calcium and thus seek out bone. Radioiodine isotopes preferentially and rapidly are taken up by the thyroid. Uranium (both U-235 and U-238) targets the kidney and bone. Plutonium (Pu-239) impacts the lung if inhaled and retained there, or bone and liver if more soluble and thus absorbed and redistributed. Furthermore, plutonium's solubility is a reflection of its production source and vice versa: the more soluble precipitated nitrates being involved occasionally in industrial purification procedure accidents, while the less soluble oxides may result from accidents involving high temperature fires. The rate of distribution to each organ is related to organ metabolism, the ease of chemical transport, and the affinity of the radionuclide for chemicals within the organ. For example, due to their high protein and lipid makeup, the liver, kidney,

adipose tissue, and bone tend to selectively bind radionuclides (AFRRI, 2003).

3.3.2. Routes of intake and countermeasures

3.3.2.1. Inhalation The *inhalation pathway* is the most efficient route of uptake. Particle size affects the radionuclide intake, uptake, and retention. Particles small enough to enter the alveoli may either remain or be exhaled. Particles larger than 5 μm tend to be deposited in the upper airways, and when mobilized by the mucociliary tree, may serve as a secondary source for ingestion. The chemical form of the isotope (e.g., oxides versus nitrates) in part dictates whether it is insoluble and remains in the lungs for a long duration, or is more soluble and tends to be absorbed and redistributed. This impacts the location and duration of isotope retention that, in turn, defines where the radiation dose occurs, subsequently producing the injury (or location of pathology). For example, high-LET alpha emitters such as plutonium are linked to an increased incidence of malignancies, if given a prolonged exposure of the alveolar epithelium (Zajtchuk et al., 1989).

3.3.2.2. Ingestion When ingested, some radionuclides are absorbed poorly and are eliminated in the feces (a relative indication of insolubility). Some, such as radium and strontium, are absorbed partially and also may be excreted in the urine, reflecting their greater solubility. Others such as Cs-137, iodine, and tritium are absorbed readily. A radionuclide traversing the GI tract may produce damage to specific sections of the intestine and adjacent structures in proportion to the time spent at each location, and in accordance with the mean transit times as follows: stomach (1 h), small intestine (4 h), upper large intestine (13–20 h), and lower large intestine (24 h). However, the non-absorbable alpha emitters do not tend to cause gastrointestinal injury (Zajtchuk et al., 1989).

3.3.2.3. Percutaneous absorption/wounds The skin is impermeable to most radionuclides, a notable exception being tritiated water (³H₂O). However, wounds and burns create a pathway for particulate contamination to bypass the epithelial barrier. Wounds must be cleaned carefully and debrided if radiological contamination is present. Fluid in the wound may block transmission of weak beta and alpha decay emissions, thus hiding them from detectors during radiological patient surveys.

3.3.3. Medical evaluation and treatment

The medical evaluation of radiological injury is a cooperative venture among specialists. The health physicist can aid the health-care provider in estimating the maximum body burden and lifetime dose extrapolation as part of an ongoing risk-benefit analysis of treatment options. In the United States, sources of guidance on the assessment of internal contamination include the National Council on Radiation Protection and Measurements (NCRP) Report Number 65, Management of Persons Accidentally Contaminated with Radionuclides, and other references. NCRP Report Number 87, Use of Bioassay Procedures for Assessment of Internal Radionuclide Deposition,

provides additional guidance. Excretion sampling may include baseline and periodic or 24-h urine/stool collection, depending on radionuclide. Exact and complete specimen labeling is mandatory. As a rule, begin fecal sampling 24 h after exposure (unnecessary for tritium) and urinary sampling 24 h after exposure (12 h for tritium, 2–3 weeks for plutonium). Timing and duration of sampling for other isotopes may vary, and consultation should be obtained (NCRP 65, 1980).

The goal of medical treatment is to reduce both the absorbed radiation dose and the effects of chemical toxicity, thereby decreasing the risk of near-term as well as future biological effects (AFRRI, 2003). Radionuclide dose-reduction steps include efforts to reduce intake, block distribution, reduce deposition, and increase excretion. In the event of inhalation exposure, potential treatment considerations include the use of nasal irrigation (after collection of the screening specimens) and lavage, systemic treatment including chelation, and possible lung lavage. Radionuclide ingestion may be managed by gastric lavage and emetics to empty the stomach, possibly followed by purgatives, laxatives, and enemas to reduce the radionuclide residence time in the intestine and colon. Ion-exchange resins may limit gastrointestinal uptake. For example, Prussian blue (PB) is an ion-exchange chemical indicated for the management of cesium or thallium exposures. It is a prescription drug with dosage 3 g orally, 3 times daily, for adults, and 1 g orally, 3 times daily for children 2–12 years of age. PB reduces Cs-137 biological half-time by more than 70%. PB was FDA approved in 2003 and is contained in the U.S. National Strategic Stockpile (USDHHS et al., 2003).

Agents administered to acidify or alkalinize body compartments may decrease uptake, impact mobilization, and enhance elimination via urine or feces. Use of diluting and blocking agents may enhance elimination. Diluting agents flood the body with the stable isotope to both reduce uptake into the critical organ and enhance elimination. To treat tritium exposure, dilute the radionuclide with tap water by forcing fluids for 3 days. Blocking agents saturate the critical organ with the stable isotope if taken early enough. For example, with radioactive iodine (I-125, or I-131, etc.) one may administer the stable isotope potassium iodide (KI). Iodine adult prophylaxis management is, as indicated in the U.S. FDA guidance (Table 2), stratified by estimated radiation dose exposure level (Gy) and age. The new FDA guidance released in December 2001 lowered the exposure thresholds for KI prophylaxis and lowered the doses of KI for neonates, infants, and children (see details at <http://www.fda.gov/cder/guidance/4825fnl.pdf>). Previous guidance was for an adult dose of 130 mg KI orally a day for 7–14 days, pre-exposure, or 390 mg KI within 30 min post-exposure (repeat daily if continued exposure). Previous pediatric guidance was based partly upon various external thyroid irradiation-exposure data suggesting an action level at 0.25 Gy or more for children.

The FDA revised the KI dosing and action levels in part as a result of case control study evidence of a quantified cause-effect relationship between thyroid radioiodine deposition and thyroid cancer risk from studies of the Chernobyl accident. Unlike previous thyroid radiation exposures, the iodine

exposures from Chernobyl were almost all internal contamination cases, due to radioiodines, resulting in a sharp increase in thyroid cancer incidence in the exposed pediatric population, occurring approximately 4 years after the accident. The majority of thyroid cancer cases occurred in children receiving thyroid doses estimated to be less than 0.3 Gy, with a marked increase in thyroid cancers in children exposed at 0.05 Gy or more. A KI dose protects for about 24 h. Daily dosing is indicated until the risk of significant exposure ends. Side effects of repeated doses of KI may include iodine-induced thyrotoxicosis in the aged or iodine deficient. Iodide goiter and hypothyroidism may occur but generally require chronic high doses of KI. Individuals, usually adults, with multinodular goiter, Grave's disease, and autoimmune thyroiditis must be treated with caution if dosed for more than a few days. Individuals intolerant of KI, as well as neonates, and pregnant and lactating women should have priority for protective measures such as sheltering, evacuation, and uncontaminated food and water. Repeat dosing of neonates should be avoided to minimize the risk of hypothyroidism during that critical phase of brain development. If treated with KI, neonates should be monitored for hypothyroidism by measuring TSH, and FT4 if indicated, while being prepared to institute thyroid hormone therapy if needed. Due to the risk of blocking fetal thyroid function, repeated dosing of pregnant women should be avoided. Repeated dosing of lactating women poses a risk of hypothyroidism in the nursing neonate, and should be avoided except during continuing severe contamination (with monitoring as described above). In general, the Chernobyl exposures were assessed as occurring largely via contaminated cows' milk and from inhalation by those residing near the accident or otherwise receiving a large plume dose (USDHHS et al., 2001).

Treatment with mobilizing or chelating agents should be initiated as soon as feasible, assuming the exposure is estimated to be significant. Chelating agents include edetate calcium disodium (Ca-EDTA) (for lead and other metals), diethylenetriaminepentaacetate (DTPA) (for transuranics/rare earth metals), deferoxamine (for iron and plutonium), and penicillamine (for copper, iron, mercury, lead, and gold). DTPA (as trisodium calcium or zinc salts) is indicated for treatment of contamination with plutonium, americium, or curium to increase the rates of elimination. Adult dose is 1 g per day, infused IV over 1–2 h in normal saline or 5% glucose. Treatment is begun empirically with a history of inhalation exposure, and continued based upon accurate dose assessment and urinary excretion levels. Urine specimens are required before and during therapy. Rare side effects include nausea, vomiting, diarrhea, fever, pruritis, and induced mineral deficiency. Cited contraindications include renal insufficiency, pregnancy, hypercalcemia, and oral radionuclide intoxication. DTPA is water soluble, stays in extracellular fluids, does not complex "insoluble" particles, and works over a 2- to 3-h period. It removes 60–90% of soluble plutonium (Pu) if given within 3–12 h. Initial treatment is with the DTPA calcium salt followed by use of the zinc salt in subsequent administrations to preclude zinc depletion. DTPA was FDA approved in 2004 and is available in the U.S. Strategic National Stockpile. Other agents and examples of their treatments include cobalt

Table 2
Food and Drug Administration guidance, potassium iodide (KI) as a thyroid-blocking agent in radiation emergencies (December 10, 2001)

Threshold thyroid radioactive exposures and recommended doses of KI for different risk groups				
	Predicted thyroid exposure (Gy)	KI dose (mg)	Number of 130-mg KI tablets	Number of 65-mg KI tablets
Adults over 40 years	≥5	130	1	2
Adults, 18–40 years	≥0.10			
Pregnant or lactating women	≥0.05			
Adolescents, 12–18 years ^a		65	1/2	1
Children, 3–12 years				
1 month–3 years		32	1/4	1/2
Birth–1 month		16	1/8	1/4

Thyroid gland dose action levels for KI administration to protect against thyroid cancer risk:

- 0.05 Gy or more: children aged 0–18 years and pregnant or lactating women.
- 0.1 Gy or more: adults up to 40 years.
- 5.0 Gy or more: adults over 40 (to prevent hypothyroidism).

^aAdolescents approaching adult size (≥70 kg) should receive the full adult dose (130 mg).

(GI lavage, penicillamine, EDTA); uranium (DTPA, alkalize urine, MgSO₄); radium (alkalinize, MgSO₄, lavage/purge); and strontium (alginates, acidify urine). Also against strontium (Sr-85, Sr-90) one may use calcium, aluminium, barium sulfate (to block intestinal absorption), and strontium salts.

A risk-benefit analysis is required, especially before proceeding with some forms of treatment, such as pulmonary lavage or certain chelation scenarios, involving increased risk to the patient.

3.4. Management of cutaneous radiation syndrome (CRS)

Radiation accidents that involve localized irradiation to small parts of the body are much more frequent than those that result in whole-body radiation. Generally, when there is significant whole-body radiation, there is significant local radiation injury, primarily cutaneous injury (Gusev et al., 2001).

In general, cutaneous injury from thermal or radiation burns is characterized by loss of epidermis and, at times, dermis. Injuries to the skin may cover small areas but extend deep, even into muscle and bone. Skin injury may be accompanied by profound local edema and place the patient at risk for a compartment syndrome. Patients presenting with burns immediately after exposure have thermal rather than radiation burns. Significant injuries to the integument decrease the LD_{50/60} and increase the risk for death at any radiation-exposure dose. Patients with the hematopoietic syndrome and cutaneous injury will have a more complicated course of both. Appropriate treatment of cutaneous radiation injury may require multi-modality care as provided by a burn center. Multiple surgical procedures may be necessary, and duration of care may be quite prolonged. Peter of the University of Ulm, Germany, has divided CRS into five time-related stages: prodromal erythematous, manifestation, subacute, chronic, and late. Each stage has different manifestations and appropriate treatment. The prodromal stage may occur within several minutes to a few hours after exposure, and is manifested by redness and itching. This disappears, and then

Table 3
Threshold skin doses for various skin injuries

Effect	Dose (Gy)	Time to onset
Early transient erythema	2	Hours
Mainly erythema	6	~ 10 days
Temporary epilation	3	~ 2 weeks
Permanent epilation	7	~ 2 weeks
Dry desquamation	14	~ 4 weeks
Moist desquamation	18	~ 4 weeks
Secondary ulceration	24	> 6 weeks
Late erythema	15	~ 8–10 weeks
Ischemic dermal necrosis	18	> 10 weeks
Late dermal necrosis	> 12	> 1 year

erythema and pruritus along with tissue damage can manifest after 3 weeks (Gottloeber and Peter, 2002). The late phase may not occur for more than 20 years after an incident and present with angiomas, keratoses, ulcers and squamous- and basal-cell carcinomas (Peter, 1996). Itching and redness in the prodromal and manifestation stages can be treated by cooling lotions and non-atrophogenic topical steroids. Pentoxifylline appears to improve active and passive range of motion after radiation injury to soft tissue (Okunieff et al., 2004), and also to reduce radiation-induced fibrosis (Delanian et al., 2003) (Table 3).

4. Gaps

4.1. Priority research areas

The U.S. Radiological/Nuclear Threat Countermeasures Working Group recently published a priority list of research areas for radiological- and nuclear-threat countermeasures (Pellmar et al., 2005). This publication recommends the following priorities for research.

Top priority:

1. Radioprotectors for use prior to exposure.
2. Therapeutic agents for post-exposure treatment.

3. Antimicrobial therapy for infections associated with radiation exposure.
4. Cytokines and growth factors.
5. Mechanisms of radiation injury at the molecular, cellular, tissue, and organism levels.
6. Automation of biodosimetric assays for high throughput.
High priority:

1. Developing biomarkers for biodosimetry.
2. Enhancing training in the radiation sciences.
3. Exploring the consequences of combined injury.
4. Establishing a repository of information regarding investigational countermeasures.
5. Following the health of an exposed population to better prepare for subsequent events.

Medium priority:

1. Develop novel approaches using progenitor cells.
2. Develop improved decorporation therapies.
3. Develop approaches to mitigate the psychological impact of a terrorist event.
4. Develop animal models for the assessment of radiation injury and evaluation of countermeasures.

Low priority:

1. Research to understand the mechanisms of radiation-induced cellular and tissue injury that lead to cancer.
2. Conduct epidemiological studies to acquire scientific evidence regarding the long-term health effects of ionizing radiation.

4.2. Potential near-term radiation injury countermeasures

4.2.1. General radioprotection

Several dietary supplements, including glutamine, vitamin A, vitamin E analogues (tocopherols and tocotrienols), selenium compounds, sulphur, and zinc have shown promise in some studies by functioning as free radical scavengers. The advantages of these compounds are that they generally are non-toxic and can be taken orally.

Aminothiols affect radiation-induced changes in gene expression, carcinogenesis, and mutagenesis. The aminothiol, amifostine (Ethyol[®]), is approved for use in protecting normal tissue in radiation therapy patients, but is too toxic for use in first responders and receivers. Eicosanoids may inhibit prostaglandin synthesis and provide some protection against intestinal tract injury.

4.2.2. Antiemetics

Palonosetron is an intravenous 5-HT₃ antagonist with longer half-life and higher receptor-binding affinity than similar drugs. It was approved by the U.S. FDA in July 2003 for the indication of acute or delayed nausea and vomiting associated with moderately or highly emetogenic chemotherapy. It should not be given more than once every 7 days.

Aprepitant is a P/neurokinin 1 (NK-1) receptor antagonist that is given orally once daily for 3 days. It was approved by the

U.S. FDA in March 2003 and is indicated, in combination with other antiemetic agents, for the prevention of both acute and delayed nausea and vomiting associated with highly emetogenic chemotherapy (USDHHS et al., 2006).

4.2.3. Mucositis

Palifermin (keratinocyte growth factor) was approved by the U.S. FDA in December 2004 for the indication to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy that requires hematopoietic stem cell support. Palifermin is an intravenous medication that attaches to the keratinocyte growth factor receptor and then is believed to stimulate cell growth (USDHHS et al., 2006).

4.2.4. Regeneration of hematopoietic tissue

The adrenocortical steroid 5-androstenediol (5-AED) stimulates cytokine expression, myelopoiesis, and enhances infection resistance in both normal and irradiated mice, improving survival in the latter. Phase I safety testing in humans has been initiated.

Immunomodulators such as glucans and bacterial cell wall extracts have shown some promise in prophylaxis against radiation injury in animal models, but so far have not been of benefit post-exposure.

4.2.5. Vascular perfusion/fibrosis amelioration

Heparin and other anticoagulants have been used in radiation injury treatment in the former Soviet Union with some success, particularly in preventing or mitigating cutaneous radiation injury.

Pentoxifylline has little effect in ameliorating acute radiation injury, but has been shown in rodent models to improve vascular perfusion and decrease late fibrotic effects in muscular and pulmonary tissue. Interferon gamma has also been recommended in this context (CDC, 2006b).

5. Conclusion

Medical management of radiation injury is complex. Radiation injury can present with varying degrees of the acute radiation syndrome (ARS), internal contamination, and/or cutaneous injury. Multiple organ dysfunction may occur. Treatment may require prolonged care. Mass casualties could exhaust resources. Treatment of both the acute deterministic effects of radiation injury and the long-term stochastic sequelae of radiation damage are areas ripe for research. There are several promising agents on the horizon that may, after further study, prove of value in protection prior to exposure, controlling the symptoms of ARS, improving infection control, and mitigating late term injury. Recently the LD₅₀ with treatment has increased because of improving measures against infection and stimulating hematopoietic system regeneration. However, patients have experienced hematopoietic recovery only to die of late complications from pulmonary fibrosis 3–4 months post-exposure. The next “quantum leap” in radiation injury

management will come when we understand better how to address this problem.

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Appendix B

List of Research Topics provided by the Committee on Medical Aspects of Radiation in the Environment

- a Determination of the mechanisms of radiation injury at the molecular, cellular, tissue and organ levels.
- b Research into the mechanisms of radiation carcinogenesis with reference to individual susceptibility and gene–environment interactions).
- c Development of animal models for the assessment of radiation injury and the evaluation of methods for treating such injuries.
- d Research into the effects of internalised radiation emitters (at both clinical and environmental levels).
- e Development of radioprotectors (for use prior to exposure) and therapeutic agents post-exposure.
- f Development of novel approaches for radiological protection and/or treatment of radiation damage using progenitor cells, cytokines, growth factors and stem cell biology.
- g Development of antimicrobial therapy for infections associated with radiation exposure.
- h Development of biomarkers and automated biodosimetric assays.
- i Determination of the mechanisms of radiation-induced injury which lead to the development of cancer and the possible interactions with other carcinogenic agents.
- j Studies of long-term health effects of radiation exposure by following the health of irradiated individuals.
- k Determination of the impact of low dose radiation exposure including that received from CT scanning on cancer induction.
- l Research into treatment modalities for exposure to high dose radiation from both external and internal sources.
- m Exploration of the consequences of combined injury from radiation and other sources (both physical and chemical).
- n Development of approaches for understanding and mitigating the psychological impact of radiation exposure.
- o Finally, resources should be available to allow radiobiology research groups in the UK to forge links with centres carrying out research into DNA repair mechanisms and also to forge similar links with the Chernobyl Tumour Bank.

6 Psychological Effects of Accidents and Incidents involving Ionising Radiation

Radiation incidents have the potential to inflict serious biological and ecological damage. Additionally, and of equal if not greater importance in terms of morbidity, their capacity to affect, profoundly, the psychosocial well-being of individuals, families and communities may exceed significantly the numbers of actual physical casualties. Aside from the known documented clinical effects of high dose and high dose rate radiation exposure, the general public's fear of radiation and misunderstanding of its dangers confound the efforts of incident management experts.

Studies of casualties from the Second World War and more recent major radiation incidents have documented the wide range of psychological symptoms. In this chapter the typical types of acute and chronic stress reactions will be described, illustrating that psychological stress can mimic the early signs and symptoms of acute radiation exposure. Aside from the difficulties this poses to initial triage assessment, it can generate acute fear and anxiety in others, including medical and emergency services personnel, thereby confounding relief efforts. Some studies suggest that the psychosocial impact of radiation incidents can persist for years (Adams et al, 2002).

Evidence from case studies of human responses to radiation incidents will be discussed in detail, to highlight lessons learned from previous incident management attempts. Emphasis will be placed on key learning points for supporting the general public and medical and emergency services personnel. Although each social and professional group will require advice and information, the content and communication style should take account of their specific needs.

6.1 Radiation incident characteristics

Research has identified four key facets of major incidents that help to determine their psychological impact (Becker, 1997): unfamiliarity, predictability, duration and rapidity.

- a **Unfamiliarity** People are most concerned with, and afraid of, threats that are unfamiliar. Radiation is an unfamiliar threat and, hence, more psychologically disturbing.
- b **Predictability** The unexpected is more psychologically disturbing than the expected, so if it is possible to warn people about the threat of an incident they should be better prepared. If an incident is unexpected, people are unable to bring to bear their normal routines and coping mechanisms for dealing with threats. If predictability is low, other people are more likely to be held culpable. Radiation incidents will generally lack predictability in time, place and magnitude. The negative impact of these factors may therefore be magnified.

- c **Duration** The longer the threat, the more likely it is that psychological adjustment will be made, although there could be cumulative negative effects for longer term threats. Radiation incidents are regarded as having long threat duration, with an uncertain future for health outcomes. However, this does allow time for planning and managing even projected negative consequences.
- d **Rapidity** Rapidity refers to what happens in response to the threat, from the point of view of those involved in it, not the speed of onset of the incident. People adjust better if they become slowly involved in an incident. Adjustment is whether individuals perceive themselves as having to hurry to save threatened lives and valuables. People would generally regard a fire as requiring a rapid response, while a radiation threat may not appear to pose immediate risk.

6.2 Unique threat of radiation

In radiation incidents, the threat to health and well-being typically comes not from something familiar and visible, but from beams of radiation and radioactive contamination neither visible to the naked eye nor perceived by other senses, such as smell, taste or skin sensation (except at very high dose rates). Knowledge about exposure is often incomplete and initially there may well be a lack of adequate scientific and medical information about the contamination. For many radiation exposure risks, the degree of danger can only be estimated. Frequently, there is uncertainty about the consequences of exposure and long-term effects may take years or even generations to manifest (Erikson, 1994). Thus, it is not at all clear to those initially affected whether the worst is over or yet to come, extending the duration of perceived victimisation. Risk perception research suggests that society in general regards radiation and nuclear facilities as more dangerous than do knowledgeable experts. Nuclear hazards are therefore more memorable and imaginable and blur the distinction between the possible and the probable.

Radiation incidents are often therefore characterised by haziness and ambiguity rather than consensus. Radioactive contamination is invisible and unknowns and uncertainties are the norm. The uneven spread of contamination means that people who live near one another may have vastly different experiences of the situation. In the face of such ambiguity, and in the context of such vital emotionally charged issues (ie long-term health risks), differing understandings and interpretations can engender controversy, conflict and social division. Whereas some people will perceive extreme threat, others may question whether any hazard exists at all.

6.3 Potential psychological impact

This long latency between exposure and late (ie mostly stochastic) disease manifestation results in prolonged anxiety for the individual and the community. Also, man-made disasters are considered by people to be preventable and hence more distressing than natural disasters that are seen as caprices of nature or 'acts of God'. Technological disasters, being of human manufacture, are, at least in principle, preventable so there is always a moral to be drawn, always a share of blame to be assigned (Becker, 1997).

After an accident, people want to know why something that need not have happened has indeed taken place, why suffering that could have been avoided has happened, and so, rather than giving rise to acceptance or resignation, accidents/incidents give rise to anger and outrage. The conviction that the authorities, who are meant to protect the public, failed to do so can generate a powerful sense of violation and betrayal. In the aftermath, lingering mistrust can extend to any institution perceived as linked to the incident, and official bodies and personnel in general, seriously hampering organised assistance efforts (see, for example, Lacey, 1972).

6.4 Typical types of stress/strain reaction

Strain in response to an external stressor is composed of physical and psychological changes in individuals that are closely interlinked. Psychosomatic reactions can produce real physical changes and actual physical ailments, such as digestive and circulatory system complaints (see, for example, Smith, 1993). Actual injuries, such as cutaneous radiation injury, can also increase arousal and anxiety, creating a positive physiological and psychological feedback loop fuelling further distress (Chinkina, 1991).

6.4.1 Acute stress disorder

Acute stress disorder (ASD) is a condition that has only been named as such since 1994. It refers to a response to exposure to a traumatic event that results in serious impairment in terms of social, occupational or other key effects that seriously debilitate a person from functioning normally. Onset can occur within 2 days of exposure and lasts no longer than 28 days (American Psychiatric Association, 2000). Symptoms of ASD include dissociation, anxiety/increased arousal, persistent re-experiencing of the trauma and avoidance of reminders about traumatic event.

Those at risk of developing ASD include people immediately injured, relatives and friends of the injured, particularly children, rescue workers and medical personnel treating the injured. Children have less developed defence mechanisms and poorer communication skills to express their intense emotions and fears.

6.4.2 Severe fear reaction

The media portrayal of mass public panic is rare in case studies of actual large-scale incidents (see, for example, Robson, 1973). What may be observed is a type of extreme fear reaction. Instead of panic, people become disorganised, particularly if their normal frames of reference have been destroyed. They become confused and at a complete loss as to what they should do. If the incident is particularly devastating, with significant loss of life, the horror of the situation can be so overwhelming that they cease to function as effective individuals. Accounts of the injured survivors of the atomic bombing of Nagasaki describe them as wandering in complete silence, or with a low moan – long files of people processing slowly with no sense of direction or show of emotion (see, for example, Akizuki, 1981).

6.4.3 Later psychological symptoms

A common symptom experienced some time after the event is survivor guilt. Those who survive a major incident try to make sense of their survival, despite the demise of others. Being unable to attribute their survival to chance, survivors often convince themselves that they survived because others perished. Sometimes they feel guilt for being the only surviving member of a family, or guilt at leaving others, perhaps injured, behind. Such guilt can remain for decades (see, for example, Lifton, 1967).

Psychosomatic symptoms can develop into a self-fulfilling prophecy, whereby if a person believes that they are ill, they will become ill. Research from both laboratory and field studies has repeatedly demonstrated that anxiety can increase corticosteroid production, and that in turn can lead to reduced immune system function (see, for example, Frankenhauser, 1989). For radiological disasters, rumours about the threat of long-term ecological contamination and chronic health defects can exacerbate the impact of psychosomatic symptoms to the extent that every minor ailment is perceived as a potential indicator of personal catastrophe.

Physiological responses to threat can involve one of two pathways to increased neuroendocrine production – one that is energising to meet a challenge, the other debilitating. Increased corticosteroid production is triggered by novel or unfamiliar challenges, such as a radiation incident. This can produce physiological and psychological distress but without energising the individual to act and neutralise the perceived threat. If this reaction persists, it can lead to a negative feedback loop to further distress and the development of a hopeless/helpless spiral whereby the individual feels unable to cope with even routine day-to-day tasks (Seligman, 1975). Chronic corticosteroid production can result in known detrimental effects on an individual's ability to fight infection, and an increased risk of heart disease and stomach ulcers (see, for example, Stansfield and Marmot, 2002).

6.4.4 Post traumatic stress disorder

Post traumatic stress disorder (PTSD) refers to the continuation of ASD symptoms beyond one month's duration (American Psychiatric Association, 2000). Acute PTSD is defined as between one and three months' duration, whilst chronic PTSD refers to symptoms persisting in excess of three months. Onset may be delayed for months, even years, after initial exposure to the trauma. The key distinguishing feature of PTSD is where symptoms become persistent and intrusive, preventing an individual from normal daily functioning. Key predisposing factors are previous mental illness and previous exposure to trauma. Key preventive factors are good social support and firm religious or sense-making beliefs about the world.

6.5 Case studies of human behavioural responses to radiation incidents

6.5.1 Second World War, Hiroshima and Nagasaki

The first mass radiation exposure resulted from the atomic bombings of Hiroshima and Nagasaki in August 1945. The data here are not directly applicable to how the British public would behave now, because the nation is not at war, expecting a devastating attack. In Japan, in the 1940s there was little public knowledge of radiation and the Japanese were at war, expecting to be bombed by the Allied Forces. The attack, therefore, was not unexpected, only the degree of devastation and the baffling symptomatology of the survivors. The different cultural values of the Japanese must also be taken into account, as these influenced their immediate coping strategies and longer term adaptation.

As for the psychological impact, the context of war and different cultural values make it difficult to translate this experience to the UK. In addition, the Japanese did not possess the extensive contemporary knowledge of psychological trauma and many cases will not have been diagnosed. The diary of Japanese physician Michihiko Hachiya (1955) provides a particularly graphic account of the symptoms of the injured. In terms of physical health effects, large whole body doses of radiation resulted in brain damage, headaches, fever, nausea, vomiting, diarrhoea and subcutaneous haemorrhage. The main delayed symptom was somnolence. Many of these symptoms are remarkably similar to acute anxiety, rendering differential diagnosis problematic.

‘Immediate casualties were caused by the combined effects of thermal rays. The majority of people within 2 km of the hypocentre sustained serious physical injuries. Most civic and residential buildings were destroyed; city functions and socioeconomic conditions were significantly disrupted. The immediate and overwhelming mortality and morbidity and whole-scale environmental devastation plunged the survivors into an irresolvable encounter with death. Of the survivors, many were injured, had lost their families and suffered the collapse of their economic wherewithal. In an instant, survivors saw their entire world, not just their city, destroyed. It is therefore not hard to understand why they distrusted the “all-clear” ’ (Lifton, 1967). Subsequently, the survivors, in addition to their suffering from the physical sequelae and anxiety over their fates and prospects, suffered for a long time from poor physical living conditions and an absence of social support. These factors had complex physical and psychological effects upon the survivors, and resulted in increased depression and anxiety about cancer, fears of death and dying, and generalised complaints of fatigue, dizziness, irritability and difficulty coping (Yamada et al, 1991). There is no evidence of an increase in suicides following radiation exposure, although this may be masked by the prevailing cultural values at that time.

6.5.2 Atomic veterans syndrome

Between 1946 and 1962 approximately 250,000 American military personnel were exposed to atmospheric nuclear tests. The nature of exposure varied. Infantry were placed in trenches one or two miles from the detonation site of a nuclear explosion. Twenty minutes after detonation, personnel were ordered to march to ground zero for the purposes of conducting military manoeuvres. Other military

personnel – for example, in warships – steamed into ground zero after witnessing the explosion from the deck of a warship. The aim of these tests was to determine if military personnel were capable of functioning under post-detonation conditions (Veteran Claims for Disabilities from Nuclear Weapons Testing, 1979).

The term ‘A-bomb neurosis’ has frequently been used to describe excessive anxiety over symptoms following this exposure to radiation, and the fear of leukaemia and cancer, sometimes to such an extent that an individual’s ability to lead a normal life is significantly impaired. In extreme cases, an individual can become bedridden. The majority of atomic veterans left the service believing that their health had not been impaired by the radiation exposure. In late 1979, a significant number of atomic veterans reported developing major psychological symptoms that they believed were a result of their participation in nuclear tests. It was only when these veterans were informed about the dangers of radiation by the US Department for Defense or the media that they suspected their previous exposure could be the cause. Vyner (1983) conducted extensive case studies of eleven atomic veterans who reported developing physical illnesses that became a central issue in their lives. For four of the veterans these could have resulted from exposure to ionising radiation, and seven veterans experienced a long series of major and minor physical illnesses not considered to be linked to radiation exposure. The latter seven cases had ailments that could not be diagnosed or treated by their physicians, although the ailments were genuinely debilitating and became the focus of extensive laboratory evaluation.

Vyner (1983) concluded that the syndrome had two components: an elaborate belief system that an individual had been harmed by radiation exposure and a set of behavioural symptoms that expressed this belief. It is similar to PTSD, although it stems from the individual’s search for a meaning for a disease or ailment from which they were suffering. It is almost impossible for such individuals to prove that any illnesses were caused by radiation exposure and also determine whether they will develop further illnesses. This mystery leads to a complete preoccupation with their health. Many sufferers said they would prefer a fatal diagnosis than to continue with the anxiety and uncertainty of no diagnosis at all. They saw themselves as being different from the way they were before the exposure: healthy to unhealthy, patriotic to unpatriotic, and social to isolated and antisocial. They resolved their ill-health mystery by believing they would die of a radiation-induced disease. Sufferers had no respect for the medical profession who were perceived as unwilling and unable to help. They were angry at the government for knowingly placing them in danger and then refusing to accept responsibility. Some felt guilt over their anger. Physicians and psychiatrists have proposed three potential explanatory hypotheses for this behaviour (Vyner, 1983).

- a The syndrome is a pathological development of the self-diagnostic belief that a person has been harmed by exposure to ionising radiation, into a set of symptoms that elaborate upon and express that belief.
- b The belief develops as a means of resolving one or more medical mysteries arising after exposure to ionising radiation.
- c The development of the syndrome is a consequence of exposure to ionising radiation.

This belief system displays remarkable similarities to those surrounding Gulf War syndrome (Wessely, 2006; Pall, 2007).

6.5.3 Three Mile Island

This well-documented industrial accident started at 04.00 hours on 29 March 1979 when several water pumps malfunctioned in the Three Mile Island (TMI) Unit 2 plant and escalated over the following few days. On 30 March, the Governor of Pennsylvania advised all pregnant women and pre-school children within five miles of the plant to evacuate and closed all schools in the area. In total, 144,000 residents were temporarily evacuated. Schools did not re-open until 10 April. The President's Commission Report on the accident (Kemeny, 1979) stated that:

‘The major health effect of the accident appears to have been on the mental health of people living in the region of TMI and the workers at TMI.’

On Saturday 31 March, the Nuclear Regulatory Commission (NRC) stated that a hydrogen explosion could occur within the TMI-2 reactor containment. This was incorrect, according to the President's Commission, and the Special Inquiry Group noted that the risk of a possible hydrogen explosion was vastly exaggerated by the disorganised response of the NRC. The communication breakdown and information crises that resulted may have caused more harm than the accident itself. During the two-week emergency period, approximately 60% of those living within five miles of the plant had evacuated and 45% of those living within ten miles had also left. These inaccurate reports rendered future information releases suspect in the minds of TMI residents who experienced a rapid reversal from one of safe containment to extreme uncertainty and vulnerability. Consequently, the credibility of officials suffered irreparable harm.

A number of longitudinal psychological studies have been conducted on the TMI residents. One such randomised control study of sleep quality found that even three years after the event, sleep disturbances (in the form of nocturnal awakenings) were more common among TMI residents than control subjects (Davidson et al, 1987). Residents reporting more symptoms of stress also experienced greater sleep disturbance. Both behavioural and biochemical data suggested that reported symptoms were not due solely to TMI residents simply complaining. Researchers found higher levels of adrenaline both during the day and at night. (Levels would normally drop at night.) As adrenaline is an indicator of increased arousal, this suggests residents were experiencing chronic stress. The only question concerned the direction of causation. Had the increased anxiety resulted in poorer sleep, or was poor sleep increasing anxiety?

Field studies conducted at TMI five years after the accident included interviews with residents and a control group (Baum et al, 1983), using various psychometric and biochemical tests to assess stress and coping. As a group, TMI residents exhibited more symptoms of stress compared to controls and used denial rather than emotion-focused coping strategies. Denial was associated with more symptoms of ill-health, greater distress and poorer performance on psychometric tests.

Because TMI residents were exposed to a chance accident, the researchers postulated that their perceptions of other chance events would be affected. Using a random digit prediction test (a well-validated psychometric test) with either high or low subject control, TMI residents were found to be less persistent than the matched ‘control’ group (defeatist) and expressed a greater need for personal control. The impact of the TMI incident on residents’ coping styles and cognition shows the long lasting

impact of a chronic and episodic stressor. The lack of involvement or participation in tasks with uncertain outcomes increased feelings of helplessness, leading to apathy in everyday life – cf Seligman’s early work on learned helplessness (Seligman, 1975).

6.5.4 Chernobyl

The accident at the Chernobyl nuclear plant in 1986 is the worst disaster in the history of nuclear power and the most serious environmental contamination ever recorded, with more than 21,000 km² of land contaminated with levels higher than 37 GBq km⁻². Estimates vary, but it is reasonable to conclude that 17 million people in this region of the former Soviet Union – Belarus, Russia and Ukraine – were exposed to significant radioactive contamination. Exposure levels varied for those in the vicinity, depending on occupation, home location, length of exposure and ingestion of contaminated food. Evacuation was delayed, but in total 135,000 residents were evacuated (World Nuclear Association, 2000). In addition to those forcibly relocated, hundreds of thousands voluntarily emigrated from the former Soviet Union, when travel restrictions were lifted by the authorities. The largest ethnic group of evacuees was Jewish, 850,000 of whom left, mainly to go to Israel and the USA (Weinberg et al, 1995). A striking characteristic of these immigrants to the USA was to seek healthcare for what they believed would be long-term illnesses arising from radiation exposure (see, for example, Cwikel et al, 1997).

Numerous studies in the literature suggest that the psychological effects were most prominent in the first decade after the Chernobyl accident. Surveys in Sweden in the first few months after the disaster showed high levels of concern about radiation exposure, particularly from females and farmers (Beach, 1990). The International Atomic Energy Agency survey of residents of contaminated villages showed high levels of anxiety and distress (IAEA, 1991; Gintzberg, 1993). Despite initial concern over effects on unborn children, it appears that no real risk was present, even in areas with larger measured doses of radiation (World Nuclear Association, 2000). Despite worldwide concern to the contrary, a comprehensive review of epidemiological studies on the medical health impact concluded that, aside from 1800 cases of childhood thyroid cancer, ‘there is no evidence of a major public health impact attributable to radiation exposure 14 years after the accident’ (UNSCEAR, 2000: Annex J, p66). By contrast, the psychological consequences were acknowledged as a major problem. The longer term depression, anxiety and adjustment problems of the evacuated population were considered to be attributable not to radiation exposure itself, but to the profound social, economic and political changes subsequent to the disaster.

6.5.5 Goiânia

On 13 September 1987 a capsule filled with caesium-137 that had been abandoned in a radiotherapy clinic was stolen and broken open, contaminating part of the population and city of Goiânia, Brazil. The contamination spread through an area of 3000 m² and produced 100 tons (often cited as 3500 m³) of radioactive waste. Following the incident, 112,800 people voluntarily sought medical assessments, conducted over 15 days in an Olympic stadium. Of these, only 249 were contaminated, internally or

externally and, of those, 120 had contamination only on their shoes and clothes. The remaining 129 people had contamination on their clothes and skin, and were swiftly decontaminated. However, 46 people required treatment for internal contamination. Of the 112,800 people who voluntarily sought medical assessment, only 50 had skin contamination and 20, of whom 4 died, were hospitalised for medical care (Brandao-Mello et al, 1991).

This incident had such a profound impact that one in ten residents felt threatened enough to stand in line, miss a day of work and submit to assessment and monitoring for potential radioactive contamination. Of the 5000 people with acute stress reactions, some returned daily to be monitored. The scavenging of one capsule filled with caesium-137 required 750 professionals from the civil defence, military police and health services to successfully manage decontamination efforts.

Initially, the wider national public did not believe official communications of the low risks of contamination, resulting in discrimination of local residents. Professionals were the most discriminated against from their working colleagues in a survey conducted 9–14 months after the event (Curado et al, 1991).

Some of the less seriously ill patients expressed their anger by spreading contaminated faeces around their hospital rooms. Those with serious medical conditions expressed sadness, fear, grief, depression, guilt, physical aggression, anger, vandalism and emotional outbursts (Brandao-Mello et al, 1991).

6.5.6 Poisoning of Alexander Litvinenko

In November 2006, Alexander Litvinenko was fatally poisoned with polonium-210 in a public place in London. In response, the Health Protection Agency began a public health campaign to assess the risks to members of the public who may have been exposed. Media speculation that thousands were at risk was fuelled, in part, by reports that 33,000 British Airways passengers were at risk, overloading a dedicated BA helpline (Gardham, 2006).

The HPA attempted to reassure the general public that the risk of harm was low, although over 3800 calls were made to NHS Direct in the four weeks after the story was first reported in the media (Meara, 2007). A swift HPA monitoring strategy identified 990 people for risk assessment interviews, of whom 779 were offered a urine test, only 17 of which resulted in urine levels 'of some concern' (Meara, 2007). Prompt HPA action and a concerted daily media campaign seemed to allay public concern. In a subsequent survey of London residents, 80% of respondents thought the HPA response to the incident had been appropriate (Rubin et al, 2007).

6.6 Implications for disaster response

6.6.1 Types of assistance required

When planning for emergency assistance, there are three levels at which assistance is required:

- a the individual,
- b the immediate wider community,
- c the regional social group.

Assistance needs to take account of not only immediate contamination and likely dispersal, but also information management needs to prepare and inform the wider community to prevent stigma. In medical terms, the long latency between exposure and potential illness, as well as the psychological impact of injuries and potential exposure-induced anxiety, requires not just immediate but longer term medical and psychosocial support (cf atomic veterans syndrome).

Case studies from previous large-scale radiation incidents have shown the complex impact on the socioeconomic environment. For example, the stigma of contamination can result in falling property prices and lack of demand for services or goods, as well as the physical debilitation of injury and subsequent unemployment of those injured (see, for example, Curado et al, 1991). Finally, the crucial importance of credible and timely information management at the local, regional, national and international levels cannot be overstated.

6.7 Guidelines for disaster management

6.7.1 Information

An abundance of scientific research shows that the predominant characteristic of people caught in disasters is actively to seek information. It is true that, initially, information may be downplayed, and people may interpret ambiguous information in the most optimistic ways, but that is a psychologically adaptive response. People will seek information to resolve ambiguity and seek reassurance about the nature of the threat, its likely impact and duration, and immediate disaster planning efforts. The prevailing media image is that major incidents generate personal pathology, deviance and mass panic. This is largely a myth (Proulx and Sime, 1991). People do not tend to panic or act irrationally. They are active, pro-social and only a minority (8–30%) will be traumatised (Thompson, 1985).

Environmental psychologists have dedicated considerable effort to the study of persuasive communication, trying to establish which variables are most important in influencing message effectiveness. Classic research by Lewis (1941) demonstrated that a message is more likely to be persuasive if the communicator is trusted and respected, nowadays termed 'source credibility'. For maximum impact, the information source needs to be perceived to possess not only expert knowledge, but also honesty and integrity. This naturally rests on the reputation of the source. Advice and instructions to the general public therefore need to disseminate from a reputable expert source, whom

the public perceive to be independent from whoever or whatever is considered to have caused the incident. Government or agency spokespersons therefore need to establish their credibility as a reliable source when managing information dissemination during an incident.

Although the information needs of medical and professional groups will differ from those of the general public, the principles of expertise, trust and respect still prevail. To engage with the potentially contaminated and injured, professionals need to have faith in their chain of command that the risks to themselves, their equipment and facilities are within acceptable boundaries. The refusal of medical and emergency services personnel to treat those contaminated is not unknown (Carvalho, 1991).

The fear of exposure to radiation can, itself, produce psychosomatic symptoms, some of which mimic acute radiation exposure. This is as true for the general public as for medical and emergency services personnel. The perceptions and preconceptions about a radiation incident may be just as important as the incident itself. Appropriate, timely and credible advice and information can, therefore, be highly constructive in limiting anxiety and facilitating the operation of incident relief efforts. Engaging the cooperation of the media to encourage responsible reporting is imperative.

Simply because a warning to evacuate or take precautionary steps has been issued by an agency does not mean it will be heeded. Case studies of disasters show that people evacuate the vicinity by social group, usually a family, sometimes delaying evacuation until they have located and assembled everyone in their group (Taylor, 1990). In some cases, people have been known to travel towards the threat in an effort to locate loved ones. For example, analysis of the fire at the Summerland leisure complex, Isle of Man, in 1973 showed people maintained strong affiliative behaviour amongst family groups when evacuating (Canter, 1985). Some people will never evacuate the vicinity of the incident, even if ordered to do so. Denial can continue in some individuals up to moment of impact with the threat.

6.7.2 Intervention and support

Aside from the immediate need for clear and reliable information, the public and emergency services personnel will need reassurance about the threat, its impact on them, their families and colleagues, and immediate disaster planning efforts. This reassurance will, of necessity, need to be more extensive for those dealing with 'front-line' efforts, who are most likely to come into direct contact with contamination. Adequate public health reassurance is essential to limit generalised anxiety and reduce the demand for medical assessments, which previous radiation incidents have shown can all too easily overwhelm emergency relief efforts. Case study evidence repeatedly demonstrates that the number of people who present for testing and medical support vastly outweigh the number of people actually exposed, sometimes by a factor of 100 (see, for example, Brandao-Mello et al, 1991).

For casualties, aside from immediate triage, basic comfort and support from emergency services personnel is all too often neglected, yet desperately needed (Thompson, 1985). Reassurance and support can limit the pervasive anxiety surrounding potential exposure to contamination, reducing the likelihood of acute anxiety and subsequent stress-related symptoms and longer term illnesses (IAEA, 1991). The importance of such emotional support should be incorporated into training for medical personnel.

Depending on the scale of the incident, normal sources of social support for many people may be destroyed due to death, injury or social stigma (affecting the victims), leading to a sense of isolation. These support mechanisms will need to be replaced to facilitate an individual's positive psychological coping mechanisms. Prompt professional help, clear and credible guidance, and the speedy evacuation of the more acute and disturbed casualties will significantly contribute to a speedy return to psychological normality.

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7 Summary and Conclusions

Research into the effects of exposure to acute, high doses of ionising radiation has been carried out for over 100 years. With the widespread introduction of cancer radiotherapy in the 1920s high dose effects in normal tissues were studied more closely as these were the effects that set the limits to the size of the therapeutic doses. Research into acute whole body radiation syndromes was encouraged with the start of the nuclear age in the late 1940s and stimulated further research into related medical therapies such as bone marrow transplantation and skin grafting.

In the 1960s new radiotherapy machines and modalities began to be introduced, which used more penetrating forms of radiation such as cobalt-60 gamma rays, megavoltage X-rays and even high energy neutrons and protons. Again their introduction stimulated work to understand acute and late radiation effects of high doses on normal tissues, and this continued throughout the second half of the twentieth century in the UK and around the world. However, in the 1990s there was a shift of emphasis in the field of radiobiological research when it was considered that much of the underlying biology behind these effects was well understood.

The latest large reviews in this field appear to have been conducted some ten or more years ago. The most recent review undertaken by the National Radiological Protection Board, predecessor to the Radiation Protection Division of the Health Protection Agency, was published in 1996 (see below). In autumn 2005 the Advisory Group on Ionising Radiation (AGIR) decided that it was time to review this field to see what research was currently under way on high dose radiation effects and whether there was a requirement for further work.

To undertake this review the AGIR set up the Subgroup on High Dose Radiation and Tissue Effects. The terms of reference and further details of the working of this Subgroup are given in Chapter 1 of this report. There follows a short summary of our findings.

In Chapter 2 the detailed information already available on radiation injury in normal tissues in both human beings and animals is reviewed. This includes all of the well-documented data relating to the whole body exposure syndromes (haematopoietic, gastrointestinal and cerebrovascular) and also effects such as radiation-induced encephalopathy and myelopathy as well as the pulmonary and cutaneous syndromes. Damage to the central nervous system and to the peripheral nerves is also considered.

We have noted that a substantial amount of information is already available on pathogenesis and the development of radiation-induced normal tissue lesions but mainly with sparsely ionising radiation. However, there are still areas of controversy and uncertainty on the development of radiation lesions at the molecular and cellular levels with both low and high LET radiation. Correlations between normal tissue lesions and possible causal factors, particularly those at the molecular and cellular levels, need to be verified at the tissue and organ levels. Furthermore, the majority of the available data on normal tissue lesions are on individual tissues and almost no data exist on combined injury or using mixed radiation

fields, both of which are a more likely consequence of radiation accidents. These are fertile areas for further research.

Chapter 3 of the report focuses on particular medical practices in radiology and radiotherapy – in particular, total body radiotherapy. We have drawn conclusions on the differences between clinical and accidental exposure to radiation to the whole body and what can be learnt from the clinical experience and applied as a therapy to an accidental exposure situation. Consideration of interventional radiological procedures (particularly fluoroscopy exposure) has demonstrated that there are situations where it is possible that a radiation dose to an individual patient may not necessarily be disclosed to a subsequent clinician (perhaps a non-radiation specialist) dealing with that patient, leading to the possibility that subsequent radiation damage may be misdiagnosed or initially mistreated. We have noted recommendations relating to operating procedures and monitoring of radiation doses and the subsequent dissemination of this information to non-radiation specialists. Further we have noted the requirement to adjust medical protocols such that the absorbed dose to any skin area irradiated is kept to the minimum necessary for the clinical task to be performed. We have also noted the need for non-radiation specialists, especially dermatologists, to be aware of the potential for skin injuries in patients who have undergone such radiological procedures.

Chapter 4 concerns the types of radiation accident that have already occurred and the level of doses received by those involved in these accidental exposures. However, the bulk of the chapter is devoted to a summary of the current techniques involved in making biological dosimetry estimations. We have noted that to date most radiation accidents have resulted in just a few people being exposed but that preparations must be made for the potential for larger-scale accidents or other events. With highly irradiated patients dose information is of great importance to those clinicians entrusted with their care. The likely biological dosimetry methodologies which may be useful in the future are considered here. The chapter finishes by touching on the emerging physical methods which may be employed to estimate doses and exposures. We note that nowhere in the UK are these methodologies being researched or exploited and this would appear to be a national shortcoming.

Chapter 5 deals with the treatment of the effects of exposure to high doses of ionising radiation. In fact, a very large bibliography on this subject already exists and we have simply quoted the latest and very fine review of this subject in this chapter. However, we have also pointed out areas where we feel further work is required.

We believe that Chapter 6 is unique to reports of this nature. It considers the psychological impact of high dose accidents and incidents on both those exposed and those responsible for the rescue and treatment of the exposed individuals. The chapter opens with a consideration of a psychological risk assessment of radiation incidents and the potential psychological impact. It goes on to consider typical types of stress reaction, severe fear reactions and later psychological symptoms, including post traumatic stress disorder. A series of case studies has been reviewed, followed by consideration of the types of assistance that might be required in managing exposed people. The chapter concludes with some guidelines for disaster management.

Our main conclusion is, however, that we believe that a lot of work is required before the UK could be said to have adequate facilities to cope with a large-scale, high dose exposure accident or incident. We

have also concluded that, particularly in recent years, research into both the diagnosis and treatment of high dose tissue effects has been seriously under-funded. The number of radiation biologists and clinicians working in these fields in the UK has fallen dramatically and may now be below a critical level. We are also concerned that the UK does not have the appropriate central or local organisations in place to deal with a significant exposure event. We have, to some extent, tried to address what needs to be done in the future, in terms of both organisation and research, in our recommendations. These are contained in Chapter 8 of this report.

8 Recommendations

As noted earlier in this report, the Department of Health (DH) has already asked the AGIR for advice in the form of answers to specific questions. We have been given permission by DH to include in this report the questions asked and the interim recommendations we produced for DH in April 2007. These are included as an appendix to this chapter. The recommendations that follow here include both updated recommendations to DH as requested in response to its specific questions and recommendations to the Health Protection Agency (HPA) as set out in the terms of reference for the Subgroup.

8.1 Dosimetry

8.1.1 Existing technologies

The rapid determination of the doses that individuals have received is of prime importance in determining the treatments that should be administered following a high exposure incident or accident. Currently, the capacity to biomonitor a large number of exposed individuals does not exist in the UK. An infrastructure is required to facilitate the use of existing methods to provide sufficiently high throughput. We make the following recommendations to aid high throughput analysis using currently available methods.

- a Classical chromosomal aberration analysis on blood lymphocytes is the 'gold standard' method. It is currently the only calibrated technique available as a routine biological dosimeter. It has limited surge capacity for responding to a mass casualty event, but there are possibilities for laboratory networking. We recommend to DH and the HPA that a national network be established that could draw upon emergency support from clinical cytogenetics units. Such networks have been set up in several countries. Additionally, funding is required to facilitate the implementation of automated analysis.
- b Electron spin resonance and optically stimulated luminescence are two well-established techniques for physical dosimetry. They can be applied to a large range of common objects: credit cards, tablets, buttons, coins and so on, that people may have about them when they are exposed to radiation. The UK is exceptional in having no organisation capable of performing either technique for personal dosimetry in response to a radiation emergency. We recommend to DH and the HPA that this deficiency should be addressed.

8.1.2 Developing technologies

Research is required to optimise alternative dosimetric possibilities arising from recent research. Our recommendations here are as follows.

- a A number of phosphorylated proteins have been identified as candidate biological dosimeters of radiation. Assays using phosphorylation-specific antibodies could be applied to assess individuals up to a few days after irradiation. Of these, the γ H2AX assay looks highly promising. We recommend to DH and the HPA the development of automation of this method so that it may be used in a casualty receiving hospital environment to provide results within the hour.
- b Fundamental research has in recent years identified a number of areas which may have implications for dosimetry. Proteomic and genomic profiling on readily obtained cells, such as leucocytes, show potential for identifying expression changes that indicate exposure to radiation. Genomic profiling using specialised chips could potentially provide a rapid method for dose estimation. Proteomic profiling requires substantial further work before it can be deployed for assessing mass casualties. We recommend to DH and the HPA that these should be explored to see whether rapid practical methods can be developed for measuring exposure in suspected irradiated individuals with a view to triage and therapy.
- c We recommend to DH and the HPA that a watching brief be kept on developments in nanotechnology aimed at producing disposable chips for routine haematological analysis. This would be a field-deployable system, using handheld computers, providing differential white cell counts in about five minutes per patient.

8.2 Dealing with exposed individuals

Damage to many different organs contributes to the potential lethality following exposure to high doses of ionising radiation and practitioners in many different clinical specialities need to work together if patients are to be properly treated. We therefore recommend that DH should designate centres of capability in the appropriate fields likely to be needed in the treatment of high dose radiation exposure. These centres should have expertise in areas such as haematology, gastroenterology, immunology, dermatology, radiotherapy and plastic surgery. Nuclear medicine clinicians may also be able to contribute significant information on the effects of internal exposures. It would be most helpful to have lead clinicians designated for each centre.

Staff changes in such centres of capability are inevitable and new therapies and dosimetric and diagnostic approaches will emerge. Therefore, we recommend to DH the creation of a central unit in the UK with responsibility for producing and maintaining the following:

- a an updated list of designated centres and lead clinicians in the UK able to undertake treatment of people exposed to radiation – this might be in the form of a network of contacts,
- b an updated list of practical dosimetric procedures for immediate assessment of doses received,

- c an updated list of diagnostic and triage procedures,
- d an updated list of therapeutic procedures for different exposure scenarios,
- e access to a supply of therapeutic material with a limited lifetime (such as growth factors) – thought should be given as to whether these resources are held locally or centrally,
- f a register of appropriate overseas contacts who would be willing to offer assistance if and when required.

The central unit should be linked to the existing national emergency response organisation and its function would be to provide immediate scientific and medical advice, contacts and access to diagnostic and treatment material. Responsibility for actual treatment of patients will remain with the clinicians.

The central unit should be charged with maintaining links with international groups such as the European Blood and Marrow Transplant Group (EBMT), the Response Assistance Network (RANET) of the International Atomic Energy Agency (IAEA), and the Radiation Emergency Medical Preparedness and Assistance Network (REMPAN) of the World Health Organization (WHO). It should also maintain awareness of work being done elsewhere – for example, the US National Institutes of Health Strategic Plan and Research Agenda on medical diagnosis and treatment of radiation injuries.

8.3 Psychological effects

The incidence of psychological effects associated with radiation incidents or accidents may vary considerably depending on the context. Nevertheless it is clear that there is the potential to elicit anxiety and distress that may far outweigh (in terms of numbers) any effect of the radiation itself. Such psychological effects may result in considerable interference with the activities that rescue and security services may be undertaking. In this report we have given guidance and advice on how major incidents may be handled so as to minimise such effects. We recommend that DH take note of this advice in planning its contingency response to major incidents and accidents, and that DH make other relevant government departments aware of it. Specifically, the principles of ‘persuasive communication’ should be employed in information dissemination to prevent panic. Also, medical personnel need to be trained in recognising the signs of anxiety and acute stress, as they may so readily mimic radiation exposure. The emotional and physical consequences of radiation exposure are so interlinked that a multidisciplinary approach to patient care is essential for effective treatment.

8.4 Training

We were dismayed at the general reduction in the training facilities for clinicians in the field of treatment of radiation overdose in the UK. We are aware of initiatives from DH to increase such training following our interim recommendations and DH and the HPA have held a seminar on organising training for clinicians in this field. We recommend that DH continue to take steps to develop and maintain the appropriate skills in this area as may be required in the UK.

8.5 Research

We have already noted the small amount of basic radiobiological research (particularly animal work) that is now carried out in the UK related to high dose radiation studies and the treatment and amelioration of high dose tissue and health effects. We believe this is in part dependent on the funding levels aimed at inspiring such research efforts. We recommend that DH address whether future funding sources and levels can be more focused on this area without detriment to other important or allied research fields. We also recommend that more research be carried out on the possible use of cytokines, growth factors and mesenchymal stem cells in treating individuals exposed to radiation.

We note that COMARE has listed a number of research topics in the general area of radiation research. Among these are several that bear directly on the treatment of those exposed to high doses of radiation:

- a development of animal models for the assessment of radiation injury and the evaluation of methods for treating such injuries,
- b research into the effects of internalised radiation emitters (at both clinical and environmental levels),
- c development of radioprotectors (for use prior to exposure) and therapeutic agents post-exposure,
- d development of novel approaches for radiological protection and/or treatment of radiation damage using progenitor cells, cytokines, growth factors and stem cell biology,
- e development of antimicrobial therapy for infections associated with radiation exposure,
- f development of biomarkers and automated biodosimetric assays,
- g research into treatment modalities for exposure to high dose radiation from both external and internal sources,
- h exploration of the consequences of combined injury from radiation and other sources (both physical and chemical),
- i development of approaches for understanding and mitigating the psychological impact of radiation exposure.

A very similar list has been identified by a working group in the USA (see Chapter 5). Funding for research in these areas is highly desirable.

8.6 Role of the HPA Radiation Protection Division

The HPA Radiation Protection Division currently has a clearly defined role to play in response to nuclear emergencies. It has lately played a considerable part in the recent polonium-210 poisoning case. We recommend that the HPA should review the role it may be called upon to play in the event of a radiation accident or incident. This review should take place in the light of those recommendations we have made to the DH.

8.7 Resources

We would like to reiterate here our advice to DH and other government departments that may be affected by our recommendations, that the suggested measures are likely to require the input of significant resources and funding, not only now but in the future, so that they can be carried out and maintained. There have previously been initiatives in this area which have not been maintained because of either a lack of organisation or a lack of funding, or both, and these have proved to have been a waste of time and effort on the part of busy clinical and scientific personnel as well as a waste of the limited resources committed to these initiatives. We recommend that this should not be repeated. To the HPA we specifically recommend that, before taking on any more responsibilities in this area, it keenly review the resources on offer. We are aware that the HPA resources are already stretched and note that further work undertaken by the HPA must be seen to be adequately funded.

Appendix

AGIR Subgroup on High Dose Radiation and Tissue Effects Interim Advice to the Department of Health, April 2007

At the third meeting of the AGIR Subgroup on High Dose Radiation and Tissue Effects the secretariat was tasked with drawing up a timescale for the expected delivery and completion dates for the finalised AGIR report for circulation to members. This is problematical in that the Subgroup's report will first have to go to the main AGIR committee for approval and then to the CRCE Board for agreement to proceed to publication. The timescale for this is difficult to estimate but having held discussions with the AGIR secretariat it would seem to be possible to complete all of the various tasks for the report to be presented to the CRCE Board at its meeting in late September at the earliest.

This, however, could cause some problems with the timescale on which the Department of Health (DH) is depending for advice on the questions it raised at the second meeting of the Subgroup. The suggested way forward was that used for the advice sought by the HPA from the AGIR Subgroup on Radon prior to the finalisation of its radon report. That is, DH and the HPA propose specific questions to which the Subgroup can respond directly without waiting for the detailed scientific review required for the Subgroup to respond to the HPA.

This process has been cleared with the HPA Director and Chairman of the CRCE Board. On 2 March 2007 a meeting was held in the Department of Health which was attended by officials from DH and the HPA and both Chairmen of the AGIR and Subgroup. At that meeting DH put forward certain questions on which it would like immediate advice noting that this would allow the Subgroup more time to consider its report.

The following are the questions posed and the rest of this paper addresses answers which were agreed at the Subgroup meeting held on 26 March 2007.

Questions from the Department of Health

- a What expertise, equipment and facilities will be needed to treat patients exposed to radiation (either external or internal sources) and where is it available in the UK? How should this information be best organised?
- b What is required to aid the diagnosis of whether a patient has been irradiated or contaminated with radioactive material? What needs to be done to aid the calculation of the dose received?
- c What training needs are required to ensure that expertise in the treatment of irradiated or contaminated patients is maintained at a sufficient level? Is enough research being conducted into the radiobiology of such high dose exposures and methods by which they may be treated/remediated?

- d What are the likely psychological effects of such exposures to radiation?
- e Do we currently have enough resources to cope with patients exposed to radiation and if not what international links would be required to obtain help in the event of such exposures occurring in the near future?
- f How can we best learn how to deal with accidental or engineered exposure to radiation?

Agreed answers to the DH questions

The Subgroup's report will try to address these questions in some depth but it is possible to give some indications of how to proceed at the moment whilst awaiting the publication of our report.

The Subgroup would recommend that DH should designate centres of capability in the appropriate fields likely to be needed in the treatment of high dose radiation exposure. These centres should have expertise in areas such as haematology, gastroenterology, immunology, dermatology, radiotherapy and plastic surgery. Nuclear medicine clinicians may also be able to contribute significant information on the effects of internal exposures. It would be most helpful to have lead clinicians designated for each centre.

Staff changes in such centres of capability are inevitable and new therapies and dosimetric and diagnostic approaches will emerge. Therefore, there ought to be a central unit in the UK with responsibility for producing and *maintaining* the following:

- a an updated list of designated centres and lead clinicians in the UK able to undertake treatment of radiation exposed people – this might be in the form of a network of contacts,
- b an updated list of practical dosimetric procedures for immediate assessment of doses received,
- c an updated list of diagnostic and triage procedures,
- d an updated list of therapeutic procedures for different exposure scenarios,
- e access to a supply of therapeutic material with a limited lifetime (such as growth factors) – thought should be given as to whether these resources are held locally or centrally,
- f a register of appropriate overseas contacts who would be willing to offer assistance if and when required.

We have attached as appendices to this document preliminary lists of practical dosimetric procedures for immediate assessment of doses, potential designated centres, diagnostic and triage procedures, and where available therapeutic procedures, and overseas contacts. It is hoped more definitive versions will be included in the final report.

The function of the central unit would be to provide immediate scientific and medical advice, contacts and access to diagnostic and treatment material. Responsibility for actual treatment will remain with the clinicians.

The central unit should be charged with maintaining links with international groups such as the European Blood and Marrow Transplant Group (EBMT), the Response Assistance Network (RANET) of the

International Atomic Energy Authority (IAEA) and the Radiation Emergency Medical Preparedness and Assistance Network (REMPAN) of the World Health Organization (WHO).

Research

The Subgroup has already noted the small amount of basic radiobiological research (particularly animal work) which is now carried out in the UK related to high dose radiation studies and the treatment and amelioration of high dose tissue and health effects. We believe this is in part dependent on the funding levels aimed at inspiring such research efforts. We recommend that government address whether future funding sources and levels can be more focused on this area without detriment to other important or allied research fields.

In contrast, fundamental research has in recent years thrown up a number of areas which may have implications for the Subgroup's work, namely signal transduction processes, changes in gene expression, and binding of repair and other proteins to DNA occurring in irradiated cells. These should be explored to see whether rapid practical methods can be developed for measuring exposure in suspected irradiated individuals with a view to triage and therapy.

Training

The Subgroup was dismayed at the general reduction in the training facilities for clinicians in the field of treatment of radiation overdose in the UK. We are aware of initiatives from DH to increase training in this field and we are attempting to find out how these initiatives are progressing and can be expedited. However, we recommend that government as a whole may need to reconsider its input into maintaining the appropriate skills in this area as may be required in the UK.

Psychological effects

The Subgroup feels it is not possible, at this time, to advise on the psychological factors that may result from such radiation exposures. It will be addressing this complex field in some depth in its report and would ask DH to defer this question (although its importance has been noted) for the time being.

Summary

In summary, the Subgroup would like to emphasise to DH and other government departments affected by our recommendations that these suggested measures may require the input of significant resources and funding, now and in the future, so that they can be carried out and maintained. We wish to note that there have been initiatives in this area previously which have not been maintained because of either a lack of organisation or a lack of funding, or both, and that these have proved to have been a waste of time and effort on the part of busy clinical and scientific personnel as well as the limited resources committed to these initiatives and that this should not be repeated.

Glossary

Absorbed dose The quantity of energy imparted by ionising radiation to a unit mass of matter such as tissue. Absorbed dose has the units of joule per kilogram (J kg^{-1}) and the specific name gray (Gy), where $1 \text{ Gy} = 1 \text{ J kg}^{-1}$.

Acute radiation syndrome Otherwise known as 'radiation sickness', it is a spectrum of responses involving haematopoietic, gastrointestinal and cerebrovascular reactions to a large radiation dose received acutely or sub-acutely to all or most of the body. It follows a dose-dependent clinical course divided into prodromal, latent and manifest periods of illness.

Ataxia A neurological sign and symptom consisting of gross incoordination of muscle movements. Ataxia is an aspecific clinical manifestation implying dysfunction of parts of the nervous system that coordinate movement, such as the cerebellum. Several possible causes exist for these patterns of neurological dysfunction.

Atrophy The partial or complete wasting away of a part of the body. Causes of atrophy include poor nourishment, poor circulation, loss of hormonal support, loss of nerve supply to the target organ, disuse or lack of exercise, and disease intrinsic to the tissue itself.

Cerebrovascular Appertaining to the blood supply of the brain.

Clastogen A chemical or physical agent that can cause breaks in chromosomes, leading to parts of the chromosome being deleted, added or rearranged.

Criticality The state of fissile material when it is undergoing a self-sustaining chain reaction. Criticality accidents occur when a nuclear chain reaction accidentally occurs in fissile material, such as enriched uranium or plutonium. People irradiated will be exposed to a mixed field of neutron and gamma radiation.

Cutaneous Appertaining to the skin.

Cytokines A category of less-widely-known signalling proteins and glycoproteins that, like hormones and neurotransmitters, are used extensively in cellular communication. While hormones are secreted from specific organs to the blood, and neurotransmitters are related to neural activity, the cytokines are a more diverse class of compounds in terms of origin and purpose. They are produced by a wide variety of haematopoietic and non-haematopoietic cell types and can have effects both on nearby cells and throughout the organism, sometimes strongly dependent on the presence of other chemicals. Cytokines are critical to the functioning of both innate and adaptive immune responses. They are often secreted by immune cells which have encountered a pathogen as a way to activate and recruit more immune cells and increase the system's response to the pathogen. However, apart from their role in the development and functioning of the immune system, as well as their aberrant modes of secretion in a variety of

immunological, inflammatory and infectious diseases, cytokines are also involved in several developmental processes during embryogenesis.

Desquamation An acute reaction to radiation exposure that describes a stage of erythema whereby the skin surface is usually shed, inflammation occurs and in some cases a serous discharge may also occur. Therefore it may be 'dry' or 'moist' in nature. Recovery of the skin normally occurs within four weeks of completion of radiation exposure.

Diagnostic radiography A term usually applied to the use of ionising radiation in medicine for identifying disease or injury in patients. Sometimes also referred to as 'clinical or diagnostic imaging', although these terms can also include the use of non-ionising radiation.

Dicentric chromosome An aberrant chromosome having two centromeres. It is formed when two chromosomes are broken by a clastogenic agent such as ionising radiation and misrepaired to form a single structure bearing the centromeres from the two original chromosomes.

DNA A long bistranded polymer, in the form of a double helix, DNA is made up of simple units called nucleotides, joined together by a sugar phosphate backbone. Attached to each sugar is one of four types of molecules called bases (adenine, thymine, cytosine and guanine). This constitutes the genetic material of organisms. The sequence of these four bases along the backbone encodes information which determines the composition and properties of the organism. The simplest organisms such as bacteria have nearly five million bases in their genetic material; human beings have more than three-hundred million bases.

Dose A measure of the amount of radiation received. More strictly it is related to the energy absorbed per unit mass of tissue (see *absorbed dose*). Doses can be estimated for individual organs or for the body as a whole.

Double strand break A lesion which interrupts both strands of the DNA double helix. It is typically formed by the induction of two or more breaks in close proximity on opposing DNA strands. In contrast to most other DNA lesions, a double strand break cannot be repaired using the opposite strand as a template. Therefore, repair is more error-prone and may cause loss of genetic material, chromosomal aberrations, mutations, loss of heterozygosity and cell death.

Dyspigmentation An abnormality in pigmentation of the skin.

Effective dose Effective dose is the sum of the weighted equivalent doses in all the tissues and organs of the body. It takes into account the biological effectiveness of different types of radiation and variation in the susceptibility of different organs and tissues to radiation damage. Thus it provides a common basis for comparing exposures from different sources. It has the unit of sievert (Sv).

Encephalopathy Literally means disease of the brain. In some contexts it refers to permanent brain injury, and in others it is reversible. It can be due to direct injury to the brain, or illness remote from the brain. In medicine it can refer to a wide variety of brain disorders with very different aetiologies, prognoses and implications. For example, prion diseases, all of which cause transmissible spongiform encephalopathies, are nearly always fatal and have an infectious origin, but other encephalopathies are reversible and can be caused by nutritional deficiencies, toxins and several other causes.

Epidermis The outermost layer of the skin.

Equivalent dose The quantity obtained by multiplying the absorbed dose in gray by a factor to allow for the different effectiveness of the various ionising radiations in causing harm to tissue. It has the unit of sievert (Sv).

Erythema A reddening of the skin. The colour change arises from the presence of additional blood in dermal capillaries which have dilated. A transient erythema may occur within a few hours of a high radiation exposure. A second wave can be observed commencing one to five weeks later.

Fluorescence *in situ* hybridisation (FISH) A technique used in cytogenetics to highlight specific sequences of DNA on chromosomes. The highlighted regions may range in size from single discrete spots through to a whole chromosome. DNA probes, immunologically labelled with fluorescent dyes, are used that bind to only those parts of the target chromosome with which they show a high degree of sequence similarity. The chromosomes are then viewed with an ultraviolet fluorescence microscope.

Fluoroscopy An imaging technique involving the use of X-radiation to obtain real-time images of the internal structures of a patient for either diagnostic or guiding purposes (eg placement of a catheter). As a diagnostic tool, it is most commonly used in examinations of the gastrointestinal tract.

γ H2AX A surrogate marker for DNA double strand breaks. H2AX is one of the histone proteins in chromatin. In response to a double strand break it becomes phosphorylated and this form is termed γ H2AX. Immunofluorescence microscopy, using antibodies against the phosphorylated histone, allows visualisation of individual fluorescent foci in the nucleus, each representing a double strand break. In response to radiation, the number of foci seen increases with dose.

Gastrointestinal The whole of the digestive tract from the mouth to the anus, including the stomach and large and small intestines.

Genomic profile Describes information about the expression of all of the genes and gene variations in an individual or an organism.

Gray (Gy) The international (SI) unit of absorbed dose. One gray is equivalent to one joule of energy absorbed per kilogram of matter such as body tissue.

Haematopoietic This is a general term which covers all aspects of the process of the formation and development of the various types of blood cells and other formed elements such as platelets, within the blood. It describes the essential process which occurs in the bone marrow for producing all the cellular and particulate components of blood.

Haemorrhage Loss of blood from the circulatory system.

Hyperpyrexia An exceptionally high body temperature.

Immunosuppression Involves an act that reduces the activation or efficacy of the immune system. Some portions of the immune system itself have immunosuppressive effects on other parts of the immune system, and immunosuppression may occur as an adverse reaction to treatment of other conditions. Deliberately induced immunosuppression is generally done to prevent the body from

rejecting an organ transplant, treating graft versus host disease (GVHD) after a bone marrow transplant, or for the treatment of autoimmune diseases such as rheumatoid arthritis or Crohn's disease. This is typically done using drugs, but may involve surgery (splenectomy), plasmapheresis or radiation exposure.

Interstitial Relating to or situated in the small, narrow spaces between tissues or parts of an organ.

Ionising radiation A type of radiation that is sufficiently energetic to remove electrons from atoms in its path. In human or animal exposures ionising radiation can result in the formation of highly reactive particles in the body which can cause damage to individual components of living cells and tissues.

Irradiation Exposure to ionising radiation.

Ischaemia Local blood supply deficit.

Latent The time that elapses between exposure to a harmful agent and the clinical appearance of an effect. In the context of radiation, the term has two uses. Early on, during the acute radiation syndrome, an asymptomatic latent period is interposed between the prodromal response and the appearance of the main stage tissue and organ injuries. The term is also applied to the time between exposure and the appearance, possibly years later, of a delayed effect such as cataract or cancer.

Leukaemia A group of malignant diseases of the blood-forming tissues in which normal control of cell production breaks down and the cells that are produced are abnormal. Leukaemia (L) can be classified as either lymphoid (L) or myeloid (M) and as either acute (A) or chronic (C) (eg ALL, AML, CLL and CML). Lymphoid and myeloid refer to the type of white blood cell affected. If this is a lymphocytic cell the condition is called lymphocytic or lymphoblastic leukaemia. Myeloid leukaemias affect any of the other types of white blood cells. Acute leukaemias develop quickly and progress rapidly; chronic leukaemias are slower to develop and slower to progress.

Linear energy transfer (LET) A measure of the density of ionisation along the track of an ionising particle in biological tissue or other medium. Particles or rays of radiation are generally described as having a high or low LET, ie their tracks leave high or low density deposits of energy.

Lymphoma A malignant tumour of the lymphatic system (lymph nodes, reticuloendothelial system and lymphocytes).

Lymphocytes Types of white blood cells – although at any time only a few per cent are in the peripheral blood circulation, the majority are widely dispersed in all tissues, especially lymphatic organs and ducts. There are two broad categories distinguishable under the microscope: large granular and small lymphocytes. Both types can be further divided into functionally distinct subsets. Most large granular lymphocytes are more commonly known as natural killer cells. The small lymphocytes are the T- and B-cells, of which many subsets are identified, having various important roles in the body's immune processes.

Lysis Refers to the death of a cell by breaking of the cellular membrane, often by viral or osmotic mechanisms that compromise its integrity.

Mesenchymal stem cell These are undifferentiated multipotent cells responsible for the healing and regeneration of various tissues including the skin, GI tract and bone marrow stroma. They have been

shown to differentiate into, among others, chondrocytes, myocytes, adipocytes, osteoblasts and beta-pancreatic islets cells. They can be obtained from marrow of healthy donors, isolated and expanded in culture to a homogeneous population. To date, mesenchymal stem cells have been used to good effect in a few patients suffering severe localised radiation burns.

Micronucleus Small, rounded objects staining positive for chromatin observed in the cytoplasm alongside the main nucleus. They comprise fragments of damaged chromosomes without centromeres, or lagging whole chromosomes, that failed to segregate into the daughter nuclei at mitosis.

Myelopathy The gradual loss of nerve function caused by disorders of the spine, myelopathy can be caused directly by spinal injury resulting in either reduced sensation or paralysis. Degenerative disease may also cause this condition, with varied degrees of loss in sensation and movement.

Neutropaenia An abnormally low number of neutrophil granulocytes which are a type of white blood cell. Neutrophils usually comprise at least 50% of circulating white blood cells and provide the primary defence against infections by destroying bacteria in the blood. Therefore patients with neutropaenia are more susceptible to bacterial infections and, without prompt medical attention, the condition may become life-threatening.

Neutrophilia An abnormally high number of neutrophil granulocytes in the blood. This may be in response to a bacterial infection or indeed to any acute inflammation, so will be raised after a heart attack or other infarct. An early transient neutrophilia is commonly the first blood change noted following a large exposure to radiation.

Orphan source A sealed source of radioactive material that is no longer under proper regulatory control. It may have been misplaced, lost or stolen.

Papilloedema Relates more specifically to optic disc swelling secondary to raised intracranial pressure. Disc swelling is distinct from disc atrophy which refers to a loss of nerve fibres at the optic nerve head and which results in a pale disc. Atrophy may be primary (where it occurs without prior disc swelling) or secondary (where it is preceded by disc swelling).

Paresthesia A skin sensation, such as tingling, prickling, 'pins and needles', itching or burning, with no apparent physical cause. In the context of irradiation, paresthesia can be experienced as one of the acute reactions to a high dose.

Parenchymal cells Thin-walled cells that make up the bulk of most tissues. They are the functional parts of an organ in the body. This is in contrast to the stroma, which refers to the supporting tissue of organs.

Platelet Otherwise known as thrombocyte, it is the circulating blood cell involved in the formation of blood clots. Low levels of platelets predispose to bleeding, while high levels, often asymptomatic, may increase the risk of thrombosis. An abnormality or disease of the platelets is called a thrombocytopathy.

Pneumonitis Inflammation of the lung.

Prodromal symptoms The first phase of the acute radiation syndrome occurring within a few hours of a high dose of radiation. This phase is characterised by anorexia, nausea and vomiting. The speed of

onset and degree of severity are dose dependent. There is usually a remission of the symptoms followed by a relatively asymptomatic latent period.

Proteomic profile An evaluation of proteins in a sample of blood. This may help detect early cancer or cancer recurrence, or help predict response to treatment.

Pulmonary Relating to the lungs and respiratory system.

Radiobiology (or radiation biology) The interdisciplinary field of science that studies the biological effects of ionising and non-ionising radiation.

Radionuclide A type of atomic nucleus which is unstable and which may undergo spontaneous decay to another atom by emission of ionising radiation (usually alpha, beta or gamma).

Radiotherapy The use of ionising radiation as external beams for the treatment of disease in patients.

Sealed source Radioactive material confined within an impervious container that is designed to remain unopened. It therefore produces external irradiation such as gamma rays that pass through the container wall. Unless the containment is breached there is no contact with, or dispersion of, the radioactive material. These sources are typically used in industrial radiography and for radiotherapy.

Sievert (Sv) The international (SI) unit of effective dose obtained by weighting the equivalent dose in each tissue in the body with ICRP recommended tissue weighting factors and summing over all tissues. Because the sievert is a large unit, effective dose is commonly expressed in millisievert (mSv) – ie one-thousandth of one sievert. The average annual radiation dose received by a member of the public in the UK is 2.7 mSv.

Telangiectasia Formation of small dilated blood vessels near the surface of the skin.

Thrombocytopenia This is a reduced platelet count in the blood. There are many possible causes, including irradiation, which in essence result in platelets being lost from the circulation faster than they can be replaced from their megakaryocyte precursors in the bone marrow. The principal risk from low platelets is haemorrhage.

Tolerance Term used in radiotherapy to describe the highest dose of radiation normal tissue can sustain without permanent breakdown/damage. It is therefore the highest treatment dose achievable in any treatment regimen.

Triage The procedure whereby numbers of patients are sorted and prioritised based on the severity of their condition so that as many as possible can be treated when resources are insufficient for all to be dealt with immediately.

Unsealed source Radioactive material held in a container that can be opened to permit the contents to be removed. They therefore pose a risk of accidental spillage resulting in contamination and incorporation of radionuclides into the body. These sources are typically found in research laboratories and hospital nuclear medicine departments.

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