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ICRP Statement on Tissue Reactions
and

Early and Late Effects of Radiation in Normal
Tissues and Organs – Threshold Doses
for Tissue Reactions in a Radiation
Protection Context



Annals of the ICRP

Published on behalf of the International Commission on Radiological Protection

Aims and Scope

The International Commission on Radiological Protection (ICRP) is the primary body in protection against ionising radiation. ICRP is a registered charity and is thus an independent non-governmental organisation created by the 1928 International Congress of Radiology to advance for the public benefit the science of radiological protection. The ICRP provides recommendations and guidance on protection against the risks associated with ionising radiation, from artificial sources widely used in medicine, general industry and nuclear enterprises, and from naturally occurring sources. These reports and recommendations are published approximately four times each year on behalf of the ICRP as the journal *Annals of the ICRP*. Each issue provides in-depth coverage of a specific subject area.

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ICRP is composed of a Main Commission, a Scientific Secretariat, and five standing Committees on: radiation effects, doses from radiation exposure, protection in medicine, the application of ICRP recommendations, and protection of the environment. The Main Commission consists of a Chair and twelve other members. Committees typically comprise 10–15 members. Biologists and medical doctors dominate the current membership; physicists are also well represented.

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Annals of the ICRP

ICRP PUBLICATION 118

ICRP Statement on Tissue Reactions and Early and Late Effects of Radiation in Normal Tissues and Organs – Threshold Doses for Tissue Reactions in a Radiation Protection Context

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GUEST EDITORIAL

A LONG ROAD

In 1928, the first recommendations of the International X-ray and Radium Protection Committee (IXRPC) warned that ‘The known effects to be guarded against are: (a) Injuries to the superficial tissues; (b) Derangements of internal organs and changes in the blood’ (ICR, 1929). The measures recommended at that time included limiting working hours, avoiding unnecessary exposure, and, in some cases, the use of shielding. In these and later recommendations of IXRPC, the focus was on protection related to biological effects that were presumed to result only from exposures above a threshold.

When IXRPC was reconstituted in 1950 as the International Commission on Radiological Protection (ICRP) during the International Congress on Radiology held in London, UK, the list of effects was much expanded from that of 1928 based on the scientific evidence accumulated primarily during the Second World War. The effects considered in the 1950 Recommendations of ICRP (ICRP, 1951) included: ‘(1) Superficial injuries, (2) General effects on the body, particularly the blood and blood-forming organs, e.g. production of anaemia, leukaemias, (3) The induction of malignant tumours, (4) Other deleterious effects including cataract, obesity, impaired fertility, and reduction of life span, (5) Genetic effects.’

The following landmark statement also appeared in the 1950 Recommendations:

in view of the unsatisfactory nature of much of the evidence on which our judgments must be based, coupled with the knowledge that certain radiation effects are irreversible and cumulative, it is strongly recommended that every effort be made to reduce exposures to all types of ionizing radiations to the lowest possible level.

This statement, which suggested that deleterious effects might arise due to exposures at levels much lower than previously thought, was the starting point of an evolution that gradually led the Commission to adopt the principles that structure the current system of radiation protection.

A first consequence of this statement was the adoption, in the 1960s, of the classification of radiation effects into two general categories: ‘acute’ and ‘late’ effects. Another consequence was the elaboration of the optimisation principle in the mid-1970s to reconcile the necessary caution because of uncertainties regarding the

relationship between low doses and late effects, and the desire to maintain the viability of activities considered socially justified given the benefits they brought.

Publication 9, entitled 'Recommendations of the International Commission on Radiological Protection' (ICRP, 1966), contained the first serious discussions about effects of radiation exposure falling into the two general categories that are referred to today as 'tissue reactions' and 'stochastic effects'. Although this categorisation reflected different underlying biological mechanisms, its scope was mainly practical in nature with the aim of defining the objectives of radiation protection in a simplified way: 'to prevent acute radiation effects, and to limit the risks of late effects to an acceptable level'.

Over the following decades, the Commission has progressively enriched and consolidated its system of protection based on this categorisation, reflecting the accumulation of knowledge on effects due to advances in epidemiology and radiobiology. Over time, the terminology has evolved without fundamentally changing its basic approach of protection. A first evolution was the introduction of the distinction between non-stochastic and stochastic effects to replace the acute and late categories (ICRP, 1977), and the distinction between early and late effects for non-stochastic effects (ICRP, 1984). The next step was the introduction of the term 'deterministic' to replace the term 'non-stochastic' (ICRP, 1991). More recently, the Commission adopted the term 'tissue reactions' to replace the term 'deterministic effects' (or to use as a synonym) (ICRP, 2007).

Understanding of the mechanisms of the biological effects of radiation has progressed considerably over the last decade, as reflected in the present review. This review provides new insights into effects in the lens of the eye, and examines the best-available knowledge on radiogenic circulatory effects. Reassuringly, it found no evidence of previously unknown detrimental effects in other organs and tissues. It does not introduce any new information that alters the two complementary objectives to protect human health: 'to manage and control exposures to ionising radiation so that deterministic effects [tissue reactions] are prevented, and the risks of stochastic effects are reduced to the extent reasonably achievable' (ICRP, 2007).

The most recent scientific information concerning our understanding of radiation effects is reflected in the Statement on Tissue Reactions, also included in this publication. The new recommended equivalent dose limit for occupational exposure of the lens of the eye is based on prevention of radiogenic cataracts, with the underlying assumption of a nominal threshold at 0.5 Gy for acute or protracted exposure. Nonetheless, optimisation is explicitly recommended to aid in keeping doses below the nominal threshold, as well as to account for uncertainties in applying a nominal threshold to a population, and uncertainties in the value and even existence of a threshold.

No new limit has been recommended for public exposures to the lens of the eye, as the Commission judged that the existing limit was adequately protective, and therefore reduction of the limit could impose unnecessary restrictions. It seems highly improbable that any member of the public would receive a dose to the lens of the eye over a lifetime in excess of the nominal threshold of 0.5 Gy in a planned exposure situation considering: application of the effective dose limit of 1 mSv/year; the low likelihood of the lens of the eye being preferentially exposed for any significant period; and optimisation of protection below the equivalent dose limit for the lens of the eye.

The scientific evidence in relation to radiogenic circulatory effects is less conclusive than that for radiogenic cataract induction. Clearly, there are effects at high doses, but whether the risk of effects extends to exposures other than those found in high-dose medical procedures and exposures far above public and occupational dose limits and reference levels is not obvious. The present publication suggests that the absorbed dose threshold for circulatory disease may be as low as 0.5 Gy, with approximately 1% of exposed individuals developing cardiovascular or cerebral diseases >10 years after exposure. However, it is unclear whether or not the threshold is the same for acute, fractionated, and chronic exposures, and in the absence of evidence, it is assumed that the threshold dose is the same in all cases. Furthermore, the mechanisms are still very unclear, and even the key target organs are not known with certainty. As a result, the Commission has included a cautionary statement on circulatory effects in the Statement on Tissue Reactions, rather than introduce a new dose limit.

The present publication is certainly a milestone on the long road to full understanding of the effects of radiation on health. ICRP will continue to review new scientific studies and emerging trends systematically and thoroughly. As more is understood about the underlying mechanisms, particularly the existence of thresholds or lack thereof, it may become necessary to examine how the system of protection might evolve towards an even more pre-eminent role of the optimisation principle to take into account our expanding understanding of tissue reactions.

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ICRP Statement on Tissue Reactions

ICRP PUBLICATION 118, PART 1

ICRP Statement on Tissue Reactions

ICRP PUBLICATION 118, PART 1

Approved by the Commission on 21 April 2011

(1) The Commission issued new recommendations on radiological protection in 2007 (ICRP, 2007) which formally replaced the Commission's 1990 Recommendations (ICRP, 1991). The revised recommendations include consideration of the detriment arising from non-cancer effects of radiation on health. These effects, previously called 'deterministic effects', are now referred to as 'tissue reactions' because it is increasingly recognised that some of these effects are not determined solely at the time of irradiation but can be modified after radiation exposure. Previously, the Commission had reviewed various aspects of non-cancer health effects of low linear-energy-transfer (LET) ionising radiation in *Publication 41* (ICRP, 1984), high-LET radiation in *Publication 58* (ICRP, 1990), the skin in *Publication 59* (ICRP, 1992), and the skin and the eye in *Publication 85* (ICRP, 2000).

(2) The Commission has now reviewed recent epidemiological evidence suggesting that there are some tissue reaction effects, particularly those with very late manifestation, where threshold doses are or might be lower than previously considered. For the lens of the eye, the threshold in absorbed dose is now considered to be 0.5 Gy.

(3) For occupational exposure in planned exposure situations, the Commission now recommends an equivalent dose limit for the lens of the eye of 20 mSv/year, averaged over defined periods of 5 years, with no single year exceeding 50 mSv.

(4) Although uncertainty remains, medical practitioners should be made aware that the absorbed dose threshold for circulatory disease may be as low as 0.5 Gy to the heart or brain. Doses of this magnitude to patients could be reached during some complex interventional procedures; therefore, particular emphasis should be placed on optimisation in these circumstances.

(5) The Commission continues to recommend that optimisation of protection be applied in all exposure situations and for all categories of exposure. With the recent evidence, the Commission further emphasises that protection should be optimised not only for whole-body exposures, but also for exposures to specific tissues, particularly the lens of the eye, the heart, and the cerebrovascular system.

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Early and Late Effects of Radiation in Normal
Tissues and Organs – Threshold Doses for Tissue
Reactions in a Radiation Protection Context

ICRP PUBLICATION 118, PART 2

Early and Late Effects of Radiation in Normal Tissues and Organs – Threshold Doses for Tissue Reactions in a Radiation Protection Context

ICRP PUBLICATION 118, PART 2

Approved by the Commission in October 2011

Abstract—This report provides a review of early and late effects of radiation in normal tissues and organs with respect to radiation protection. It was instigated following a recommendation in *Publication 103* (ICRP, 2007), and it provides updated estimates of ‘practical’ threshold doses for tissue injury defined at the level of 1% incidence. Estimates are given for morbidity and mortality endpoints in all organ systems following acute, fractionated, or chronic exposure. The organ systems comprise the haematopoietic, immune, reproductive, circulatory, respiratory, musculo-skeletal, endocrine, and nervous systems; the digestive and urinary tracts; the skin; and the eye.

Particular attention is paid to circulatory disease and cataracts because of recent evidence of higher incidences of injury than expected after lower doses; hence, threshold doses appear to be lower than previously considered. This is largely because of the increasing incidences with increasing times after exposure. In the context of protection, it is the threshold doses for very long follow-up times that are the most relevant for workers and the public; for example, the atomic bomb survivors with 40–50 years of follow-up. Radiotherapy data generally apply for shorter follow-up times because of competing causes of death in cancer patients, and hence the risks of radiation-induced circulatory disease at those earlier times are lower.

A variety of biological response modifiers have been used to help reduce late reactions in many tissues. These include antioxidants, radical scavengers, inhibitors of apoptosis, anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, growth factors, and cytokines. In many cases, these give dose modification factors of 1.1–1.2, and in a few cases 1.5–2, indicating the potential for increasing threshold doses in known exposure cases. In contrast, there are agents that enhance radiation responses, notably other cytotoxic agents such as antimetabolites, alkylating agents, anti-angiogenic drugs, and antibiotics, as well as genetic and comorbidity factors.

Most tissues show a sparing effect of dose fractionation, so that total doses for a given endpoint are higher if the dose is fractionated rather than when given as a

single dose. However, for reactions manifesting very late after low total doses, particularly for cataracts and circulatory disease, it appears that the rate of dose delivery does not modify the low incidence. This implies that the injury in these cases and at these low dose levels is caused by single-hit irreparable-type events. For these two tissues, a threshold dose of 0.5 Gy is proposed herein for practical purposes, irrespective of the rate of dose delivery, and future studies may elucidate this judgement further.

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Keywords: Normal tissues; Tissue reactions; Threshold doses; Radiation responses of normal tissues; Biological response modifiers

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Reference

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PREFACE

This report was prepared by a Task Group of ICRP Committee 1 under the following terms of reference: to review and evaluate the literature on the non-cancerous effects of ionising radiation on normal tissues, both in the context of high doses received by cancer patients treated with radiotherapy or in accidents, and lower doses sustained during accidental or occupational exposures, or during other incidents of unknown magnitude. The review was instigated following a recommendation in *Publication 103* (ICRP, 2007), and the need for this was highlighted by recent reports of unexpected high incidences of cataracts and circulatory disease after low doses of radiation.

This report is not intended to present an exhaustive literature review, but rather to provide a critical evaluation of the evidence with particular reference to threshold doses for injury, which have applications regarding dose limits in radiation protection. All the main tissues and organs of the body have been considered regarding the incidence of quantitative endpoints of injury after acute, fractionated, and chronic radiation exposures, based on an analysis of the relevant human data supported by information from experimental systems. The influence of potential modifiers of the inherent radiation sensitivity of normal tissues has also been considered with respect to compounds that either exacerbate or ameliorate radiation injury, and hence their ability to modify the basic threshold doses. This report pays particular attention to recent information on cataracts and circulatory disease, where the threshold doses determined after long follow-up times appear to be much lower than considered previously.

The membership of the Task Group was as follows:

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EXECUTIVE SUMMARY

(a) The Commission issued revised recommendations for a system of radiological protection in *Publication 103* (ICRP, 2007). This included consideration of the detriment arising from non-cancer effects of radiation on health. These effects, previously called ‘deterministic effects’, are now referred to as ‘tissue reactions’ because it is increasingly recognised that these effects are not determined solely at the time of irradiation, but that many types of tissue reactions can be modified after radiation exposure. Previously, the Commission reviewed various aspects of non-cancer health effects of low linear-energy-transfer (LET) ionising radiation in *Publication 41* (ICRP, 1984), high-LET radiation in *Publication 58* (ICRP, 1990), the skin in *Publication 59* (ICRP, 1991), and the skin and the eye in *Publication 85* (ICRP, 2000).

(b) Recently, the Commission initiated a review of available scientific information on non-cancer health effects attributable to exposure to low-LET ionising radiation. ICRP stated that particular attention should be paid to radiation effects in the lens of the eye and the cardiovascular system because of recent published observations of radiation effects in these systems occurring after much lower doses than reported previously (ICRP, 2007). The full review was based on scientific articles available in the open literature. Major reviews by other organisations, in particular the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 2006), were also taken into account.

(c) The main emphasis of this review was to provide estimates of threshold dose, defined for practical purposes as the dose resulting in only 1% incidence of specified tissue or organ reactions (ICRP, 2007). The evidence arises from the effects of radiotherapeutic exposures, radiation incidents and accidents, and chronic exposures to workers or other populations. Follow-up time is recognised as very important in the case of late reactions, because the incidence of most late reactions increases, and hence the threshold dose decreases, with increasing time after irradiation. Both morbidity and mortality endpoints were considered. Many previous estimates were unchanged because of a lack of new informative data, but other estimates required modification. Section 2 is devoted to individual organ systems, first to consider the human evidence and then to support that with evidence from preclinical experimental systems. Section 3 considers the various biological response modifiers that have been used to modify radiation responses. Section 4 discusses all this information with respect to threshold doses for acute, fractionated, and chronic exposures, which are required to recommend dose limits for workers and the public. Annex A contains a series of tables of critique for each of the earlier publications concerning radiation-induced cataracts in order to provide a sound reference basis for the changes in recommended dose limits.

(d) Acute threshold doses of approximately 0.5 Gy and chronic dose rates of 0.4 Gy/year remain the recommended values for depression of haematopoiesis. Also,

for mortality, the threshold values of approximately 1 Gy acute dose without medical care and 2–3 Gy with good medical care remain unchanged from previous ICRP values. Protracted doses of 4–8 Gy in 1 week or 10–14 Gy accumulated over 1–3 months are likely to be tolerable. Growth factor administration is considered to be beneficial to help increase survival rates after radiation exposure of the bone marrow, and preclinical studies suggest that threshold doses might be increased up to two-fold by the use of good clinical support and growth factors.

(e) The acute threshold dose for early mortality at 6–9 days after intestinal irradiation is considered to be approximately 6 Gy, and good medical care is expected to increase this value. The incidence and severity of delayed intestinal radiation toxicity depends on radiation dose, volume of bowel irradiated, fractionation schedule, concomitant chemotherapy, comorbidities, and other patient factors. The threshold doses for late injury after irradiation show the greater sensitivity of the salivary glands (parotids) and the liver, for example, compared with the lower sensitivity of the rectum. The most promising enterotrophic strategies with the potential to protect the intestine from radiation injury include some cytokines, gastrointestinal peptide hormones, and a variety of nutrients.

(f) The threshold doses for the male and female reproductive systems for acute, fractionated/protracted, and chronic exposures, and the bases for these doses, remain virtually the same as those recommended previously. For male fertility, there is a trend for the threshold dose to be less for fractionated/protracted exposures compared with single exposures (reverse fractionation effect). Hormonal manipulation of spermatogenic recovery has been investigated in humans, but with little conclusive improvement. In preclinical studies, various biological response modifiers have been investigated including hormonal manipulation, antioxidants, radical scavengers, and natural compounds. However, at present, there is no over-riding conclusion that would favour one compound over others. In females, radioresponsiveness increases with age because of the decline in the size of the oocyte pool with increasing age. Although numerous studies in female patients undergoing chemotherapy (and radiotherapy) have indicated that gonadotropin-releasing hormone (GnRH) analogues might be protective of ovarian function, none of these studies were prospective randomised clinical trials, and thus the evidence was inconclusive.

(g) The salient features of the early and late radiation responses of the skin have not changed since earlier ICRP reports on this topic. The responses depend on the area of skin irradiated, dose fractionation effects, and whether the epidermis alone is irradiated or both the epidermis and the dermis. In humans, the most successful agents for reducing early reactions are anti-inflammatory compounds, and polyunsaturated fatty acids have shown promise in preclinical systems. For reducing late reactions, superoxide dismutase, fibroblast growth factor, captopril, polyunsaturated fatty acids, α -tocopherol, and inhibition of transforming growth factor-beta signalling have shown some promise in both humans and preclinical systems, with dose modification factors (DMFs) of 1.1–1.2 and a maximum of approximately 1.5.

(h) ICRP has not previously listed circulatory disease as a health hazard from radiation exposures to organs and tissues, because it is only in the last few years that

there has been greater consolidation of the evidence on this topic. The evidence arises from radiotherapeutic experience and epidemiological studies following nuclear and other radiation activities. There is no clear pattern across studies regarding whether or not the excess relative risk for cardiovascular disease is greater than that for stroke or cerebrovascular disease. From current evidence, a judgement can be made of a threshold acute dose of approximately 0.5 Gy (or 500 mSv, see note about units below) for both cardiovascular disease and cerebrovascular disease. On that basis, 0.5 Gy may lead to approximately 1% of exposed individuals developing the disease in question >10 years after exposure. This is in addition to the high natural incidence rate (circulatory diseases account for 30–50% of all deaths in most developed countries). The value of 0.5 Gy to the heart and cerebrovascular system could be reached during some complex interventional procedures. Hence, medical practitioners need to be aware of this new threshold, and should ensure that particular emphasis is given to optimisation. However, it is emphasised that there are notable uncertainties in determining the risks of these diseases at this level of radiation dose. It is unclear from available evidence whether or not the threshold is the same for acute, fractionated, and chronic exposures. For the present purposes, the threshold dose is assumed to be the same for all three types of exposure (i.e. approximately 0.5 Gy).

(i) For cataracts in the lens of the eye induced by acute exposures, recent studies, where formal estimates of threshold doses have been made after long follow-up periods, indicate values of approximately 0.5 Gy with 90–95% confidence intervals including zero dose. This is lower by a factor of 10 than deduced in earlier studies. Those studies generally had short follow-up periods, failed to consider the increasing latency period as dose decreases, did not have sufficient sensitivity to detect early lens changes using the various techniques employed, and had relatively few subjects with doses below a few Gy. For fractionated and protracted exposures, values of approximately 0.5 Gy have been similarly deduced from recent studies. However, the evidence pertaining to the latter exposures mainly refers to opacities rather than cataracts impairing vision because the follow-up times are shorter in those studies. For chronic exposure over several to many years, much of the evidence refers to minor lens opacities. Nonetheless, there is no indication that threshold accumulated doses are higher in this scenario. There are no established mitigators of lens radiation injury leading to opacities or cataracts, but lens replacement is a well-established surgical procedure.

(j) The threshold values for pneumonitis are derived from whole-lung radiotherapeutic exposures (usually 5 years of follow-up), and the values of 6.5 Gy for acute exposures and <18 Gy for fractionated exposures (2 Gy/fraction) are very similar to previous judgements. Steroids can relieve the symptoms of pneumonitis, but it remains unclear whether they can protect against the development of late fibrosis. In breast and lung cancer patients, there is some evidence for a reduction in both early and late lung toxicity when pentoxifylline was given during the period of radiotherapy, but angiotensin-converting enzyme (ACE) inhibitors had no significant effect.

(k) In the urinary tract, the kidneys are the most sensitive organ, and the bladder and the ureters are more resistant (deduced from radiotherapeutic experience, usually with 5 years of follow-up). The threshold dose for the human kidney is approximately 7–8 Gy acute dose, approaching 20 Gy for doses given as multiple 2-Gy fractions. For late reactions in the bladder and the ureters, the threshold total fractionated (2-Gy fractions) dose is ≤ 50 Gy. Anti-inflammatory agents have produced equivocal benefits in both human and animal systems. The most promising preclinical agents to date in reducing radiation nephropathy are ACE inhibitors and angiotensin II (AII) receptor antagonists. Preclinical studies have shown DMFs of 1.2–1.5 when given prophylactically from the time of irradiation.

(l) In the musculoskeletal system, radiation exposure can give rise to three different types of non-cancerous bone pathology: osteoradionecrosis, spontaneous fractures or fractures with less than normal trauma, and abnormalities of bone growth. The threshold dose for necrosis of femoral heads and rib fractures (after 5 years) is approximately 50 Gy in 2-Gy fractions, and approximately 55 Gy for skeletal muscle. In contrast to mature bone, growing bone is much more radiosensitive, and 25 Gy in 2-Gy fractions is often suggested as a critical threshold dose. Hyperbaric oxygen remains the only therapy claimed to mitigate such clinical reactions at the present time.

(m) Brain irradiation can have direct radiation effects on the thyroid and pituitary glands, as well as subtle effects on the hypothalamic–pituitary–adrenal axis and the hypothalamic–pituitary–gonadal axis. All of the information comes from radiotherapy experience using fractionated doses of (generally) 2 Gy/fraction. The hypothalamus is more radiosensitive than the pituitary. In children, radiation effects include growth hormone (GH) deficiency, precocious puberty (after lower doses) or delayed puberty (after higher doses), hypopituitarism, and hyperparathyroidism. In adults, radiation effects include hyperprolactinaemia, hypogonadism, obesity, hypothyroidism, hyperthyroidism, and adrenocorticotrophic hormone deficiency. Strategies for mitigating the effects of radiation on the endocrine system include GH replacement in children with radiation-induced GH deficiency, thyroid hormone replacement therapy in cases of its deficiency, and repeated intermittent infusion of GnRH in cases of reduced gonadotropin secretion after pituitary damage.

(n) The threshold dose for symptomatic spinal cord injury (myelitis) is approximately 50 Gy delivered in 2-Gy fractions. The injury is highly dependent on dose per fraction, and the threshold dose is greater when very small volumes (<1 cm cord length) are irradiated. The adult brain has been considered rather more resistant in terms of necrosis, but subtle effects have been detected at much lower doses of approximately 10 Gy and clear volume effects are discernable. Low-dose irradiation (1–2 Gy) to the developing brain of children can cause long-term cognitive and behavioural defects, and infants are even more susceptible with cognitive impairment in adult life detected after exposure to doses of >0.1 Gy before 18 months of age. There are no recognised mitigating agents for use in humans to treat spinal cord injury after irradiation. Preclinical studies with anti-inflammatory agents, ACE inhibitors, AII receptor antagonists, some growth factors, and polyunsaturated fatty acids have shown the most promise.

(o) This ICRP report has some changes to indicated threshold doses for tissue reactions compared with those stated in *Publication 103* (ICRP, 2007). First, the threshold dose for radiation-induced eye cataracts is now considered to be approximately 0.5 Gy for both acute and fractionated exposures, in line with various recent epidemiological studies. Second, circulatory disease has been recognised as an important late effect of radiation exposure, both for mortality and morbidity. An approximate threshold dose of 0.5 Gy has been proposed for acute and fractionated/protracted exposures on the basis that this might lead to an incidence of the order of 1% of circulatory disease in exposed individuals, although the estimation of risk at this level of dose is particularly uncertain. Third, the threshold dose values for chronic exposures depend on the exposure duration and the follow-up period after exposure. Differences between these time variables among different studies make the values more uncertain. The values quoted for both the lens of the eye and the circulatory system assume the same incidence of injury irrespective of the acute or chronic nature of the exposure over a working life, with >15–20 years follow-up time. Future studies may elucidate this further. Fourth, much more information has become available regarding the effect of biological response modifiers in mitigating tissue reactions, which has the effect of modifying threshold doses. These modifications are agent, tissue, and schedule specific, and they are likely to have increasing impact in the future, concomitant with increases in scientific and medical knowledge.

(p) Lastly, the previous ICRP judgement that acute doses up to approximately 0.1 Gy produce no functional impairment of tissues is maintained. Hence, the stochastic risks of induced cancer and hereditary effects continue to be the principal risks to consider for most applications of ICRP recommendations in occupational or public situations. However, after acute or accumulated doses of >0.5 Gy, the risk of tissue reactions (deterministic effects) becomes increasingly important, particularly for the lens of the eye and the circulatory system, at very long times after radiation exposure.

Note about units

(q) By ICRP convention, doses resulting in tissue reactions (deterministic effects) should be quoted in Gy or relative biological effectiveness (RBE)-weighted dose $RBE \cdot D$ (Gy), rather than Sv which is reserved for clearly stochastic effects. ICRP states that ‘the quantities, equivalent dose and effective dose, with their unit with the special name sievert (Sv), should not be used in the quantification of radiation doses or in determining the need for any treatment in situations where tissue reactions are caused. In general, in such cases, doses should be given in terms of absorbed dose in gray (Gy), and if high-LET radiations (e.g. neutrons or alpha particles) are involved, an RBE-weighted dose, $RBE \cdot D$ (Gy), may be used’ (ICRP, 2007). It is recognised that many doses in the literature are quoted in Sv or mSv because of previous usage and the familiarity of many professionals with this unit. Also, there is the fact that the use of a threshold model for the particular endpoints of cataract and circulatory disease remains uncertain. For low-LET radiation, the actual numerical value for either unit is the same.

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GLOSSARY

α/β ratio

A measure of the curvature of the cell survival curve and a measure of the sensitivity of a tissue to dose fractionation. Also, the dose at which the linear and quadratic components of cell killing are equal.

Absolute risk

The risk of an adverse health effect that is independent of other causes of the same health effect.

Absorbed dose

The energy imparted per unit mass by ionising radiation to matter at a specific point. The SI unit for absorbed dose is joule per kilogram (J/kg), and its special name is gray (Gy).

Accelerated fractionation

Reduction in the overall time without a significant change in dose per fraction or total dose.

Active (red) bone marrow

The organ system bone marrow contains the cell systems for the formation of blood cells starting from the pluripotent haematopoietic stem cells to the mature blood cells.

Acute radiation syndrome (ARS)

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

Adaptive response

Increased resistance of cells or tissues to radiation following a priming dose, or adjustment to radiation exposure which enables an organism to retain viability, and maintain fertility and normal functional stability of all tissues, organs, and systems under the conditions of chronic exposure. The principal criterion of radiation adaptation is an increased radioresistance (tolerance) of the organism and the cells of its critical organs.

Angiogenesis

Production of new blood vessels, mediated through tumour angiogenesis factor.

Apoptosis

A mode of rapid cell death after irradiation in which the cell nucleus displays characteristic densely staining globules, and at least some of the DNA is subsequently broken down into internucleosomal units. Sometimes postulated to be a 'programmed' and therefore potentially controllable process.

Autoimmune disease

The production of antibodies that results from an immune response to one's own molecules, cells, or tissues. Such a response results from the inability of the immune system to distinguish self from non-self. Diseases such as arthritis, scleroderma, systemic lupus erythematosus, and perhaps diabetes are considered to be autoimmune diseases.

Avalanche

Accelerating rate of cell proliferation induced by cell death.

Baseline disease rates

The annual disease incidence observed in a population in the absence of exposure to the agent under study.

Cardiac arrhythmias

Abnormally slow (bradycardia) or fast (tachycardia) beating of the heart, often attributable to abnormalities in the electrical signalling that co-ordinates the beating of the four chambers of the heart.

Cardiac valve diseases

Include a variety of abnormalities to the heart valves including mitral stenosis and tricuspid regurgitation.

Cell death

In the context of radiobiology, cell death is generally equated with any process that leads to the permanent loss of clonogenic capacity.

Clonogenic cells

Cells that have the capacity to produce an expanding family of descendants (usually at least 50). Also called 'colony-forming cells' or 'clonogens'.

Clonogenic survival

Defined as the fraction of cells that survive following exposure to, or treatment with, an agent that causes cell death. Only cells that are able to form colonies (clonogenic cells) are considered to have survived the treatment (see Cell death).

Colony

The family of cells derived from a single clonogenic cell.

Complex tissues

Cell populations in which function and proliferation take place in the same cells (otherwise called 'flexible tissues' or 'conditional renewing tissues').

Conditional renewing (complex or flexible) tissues

Tissues composed of cell populations capable of both division and function.

Confidence limits or intervals

An interval giving the lowest and highest estimate of a parameter that is statistically compatible with the data. For a 95% confidence interval, there is a 95% chance that the interval contains the parameter.

Connective tissue

The tissues of the body that bind together and support various structures of the body. Examples are bone, cartilage, and muscle.

Consequential late effects

Late normal tissue complications which are influenced by the extent (i.e. severity and/or duration) of the early response in the same tissue or organ.

Coronary heart disease/congestive heart disease

Obstruction of blood flow in the heart due to narrowing of cardiac vessels restricting blood and oxygen supply to the heart. In a mild form, this leads to angina where the reduced blood flow leads to discomfort. When blockage is severe, myocardial infarction (heart attack) occurs leading to acute heart failure.

Cytokines

Polypeptides, originally defined as being released from lymphocytes and involved in maintenance of the immune system. These factors have pleiotropic effects on haematopoietic cells and many other cell types.

D_0

A parameter in the multitarget equation: the radiation dose that reduces survival to e^{-1} (i.e. 0.37) of its previous value on the exponential portion of the survival curve.

Deterministic effect

Injury in populations of cells, characterised by a threshold dose and an increase in the severity of the reaction as the dose is increased further. Also termed 'tissue reaction'. In some cases, these effects are modifiable by postirradiation procedures including biological response modifiers.

Detriment

The total harm to health experienced by an exposed group and its descendants as a result of the group's exposure to a radiation source. Detriment is a multidimensional concept. Its principal components are the stochastic quantities: probability of attributable fatal cancer, weighted probability of attributable non-fatal cancer, weighted probability of severe heritable effects, and length of life lost if the harm occurs.

Detriment-adjusted risk

The probability of the occurrence of a stochastic effect, modified to allow for the different components of the detriment in order to express the severity of the consequence(s).

Dose modification factor

The ratio of doses with and without modifying agents causing the same level of biological effect.

Dose rate

The radiation dose delivered per unit time and measured, for example, in grays per hour.

Dose-rate effect

Decreasing radiation response with decreasing radiation dose rate.

Early normal tissue responses

Radiation-induced normal tissue damage that is expressed weeks to a few months after exposure (by definition, within approximately 90 days after onset of radiotherapy). The α/β ratio tends to be large (>6 Gy).

ED₅₀

Radiation dose that is estimated to produce a specified (normal tissue) effect in 50% of irradiated subjects ('effect dose – 50%').

Epithelium

A thin layer of cells in the skin, mucous membrane, or any duct that replaces senescent cells by cell division.

Erythropoietin

Cytokine that regulates erythrocyte levels and stimulates late erythroid progenitor cells to form small colonies of erythrocytes.

Excess absolute risk

The rate of disease incidence or mortality in an exposed population minus the corresponding disease rate in an unexposed population. The excess absolute risk is often expressed as the additive excess rate per Gy or per Sv.

Excess relative risk

The rate of disease in an exposed population divided by the rate of disease in an unexposed population, -1.0 . This is often expressed as the excess relative risk per Gy or per Sv.

Exponential survival curve

A survival curve without a threshold or shoulder region which is a straight line on a semi-logarithmic plot.

Extrapolation number

A parameter in the multitarget equation: the point on the survival scale to which the straight part of the curve back-extrapolates.

Field-size effect

The dependence of normal tissue damage on the size of the irradiated area (particularly in skin); in modern literature, typically referred to as the 'volume effect'.

Flexible tissues

Cell populations in which function and proliferation take place in the same cells (now often called 'complex tissues').

Fractionation

The daily dose of radiation based on the total dose divided into a particular number of (usually) daily treatments.

Fractionation sensitivity

The dependence of the iso-effective radiation dose on the dose per fraction. Usually quantified by the α/β ratio – a high fractionation sensitivity is characterised by a low α/β ratio (see α/β ratio).

Functional subunits

Functional subunits of tissues (e.g. nephrons in kidney, alveoli in lung).

Gastrointestinal

Having to do with the digestive tract, which includes the mouth, oesophagus, stomach, and intestines.

Gastrointestinal syndrome

The signs and symptoms of intestinal failure.

Graft vs host disease

In transplants, reaction by immunologically competent cells of the donor against the antigens present on the cells of the host. Often a fatal condition in human bone marrow transplants.

Granulocyte colony-stimulating factor

Cytokine that stimulates differentiation of progenitor cells into granulocytes.

Granulocyte-macrophage colony-stimulating factor

Cytokine that stimulates differentiation of progenitors into granulocytes, macrophages, and eosinophils.

Gray (Gy)

The special name for the SI unit of absorbed dose: 1 Gy=1 J/kg.

Growth factor

A serum protein that stimulates cell division when it binds to its cell surface receptor.

Growth fraction

Proportion of viable cells in active cell division.

Growth hormone (somatotropin)

Secreted by the anterior pituitary gland; a hormone that acts mainly on the growth of bone and muscles. Can be secreted by lymphocytes in response to phorbol ester treatment, and may be involved in lymphocyte growth.

Hierarchical tissues

Tissues comprising a lineage of stem cells, transit (amplifying) cells, and postmitotic (differentiated or mature) cells.

High linear energy transfer

Radiation with a high linear energy transfer (e.g. alpha particles, heavy ions, and interaction productions of fast neutrons). The ionisation density along the radiation track is high.

Hormones

Factors synthesised in endocrine glands that, if released, act to regulate and modulate the functions of multicellular organisms.

Hyperbaric oxygen

High oxygen pressures (2–3 atmospheres) used to enhance tissue oxygen availability in radiotherapy.

Hyperfractionation

Reduction in dose per fraction below a conventional level of 1.8–2.0 Gy.

Hypertrophic cardiomyopathy

Increased muscle density in the heart leading to less effective pumping of the blood.

Hypofractionation

The use of dose fractions larger than the conventional 2 Gy/fraction.

Hypoplasia

Reduction in cell numbers in a tissue; for example, due to radiation-induced impairment of proliferation in early-responding tissues.

Immune system

The body's defence system which protects it from foreign substances such as bacteria and viruses.

Incidence (incidence rate)

The rate of occurrence of a disease in a population within a specified period of time, often expressed as the number of cases of a disease arising per 100,000 individuals per year (or per 100,000 person-years).

Initial slope

The steepness of the initial part of the cell survival curve, usually indicated by the value of α in the linear-quadratic model.

Interphase death

The death of irradiated cells before they reach mitosis. Sometimes used as a synonym for apoptosis.

Iso-effect plots

Doses for equal effect (e.g. ED₅₀) plotted against dose per fraction or dose rate.

Late normal tissue responses

Radiation-induced normal tissue damage that in humans is expressed months to years after exposure (by definition, later than approximately 90 days after the onset of radiotherapy). The α/β ratio tends to be small (<5 Gy).

Latent time/period or latency interval

Time between (onset of) irradiation and clinical manifestation of radiation effects.

LD_{50/30}

Radiation dose to produce lethality in 50% of a population of individuals within 30 days; similarly LD_{50/7}, etc.

Lifetime risk

The risk of morbidity or dying of some particular cause over the whole of a person's life.

Linear dose response

A statistical model that expresses the risk (incidence) of an effect (e.g. disease or abnormality) as being proportional to dose.

Linear energy transfer

The rate of energy loss along the track of an ionising particle, usually expressed in keV/m.

Linear-non-threshold model

A dose–response model which is based on the assumption that, in the low-dose range, radiation doses greater than zero will increase the risk of cancer and/or heritable disease, above background levels, in a simple proportionate manner.

Linear-quadratic dose response

A statistical model that expresses the risk of an effect (e.g. disease, death, or abnormality) as the sum of two components, one proportional to dose (linear term) and the other proportional to the square of dose (quadratic term).

Linear-quadratic model

Model in which the effect (E) is a linear-quadratic function of dose (d): $E = \alpha d + \beta d^2$.
For cell survival: $S = \exp -(\alpha d + \beta d^2)$.

Neurological syndrome

Signs and symptoms of injury in the central nervous system leading to failure within 48 h.

Low linear energy transfer

Radiation with a low linear energy transfer (e.g. electrons, x rays).

Lymphatic system

A network of fine lymphatic vessels that collects tissue fluids from all over the body and returns these fluids to the blood. Accumulations of lymphocytes, called 'lymph nodes', are situated along the course of lymphatic vessels.

Macrophage colony stimulating factor

Cytokine that stimulates formation of macrophages from pluripotent haematopoietic cells.

Mitigation

Interventions to reduce the severity or risk of radiation side-effects, applied during or shortly after exposure and before clinically manifest symptoms occur (i.e. during the latent time).

Morbidity

Sickness, side-effects, and symptoms of a treatment or disease.

Multitarget equation

Model that assumes the presence of a number of critical targets in a cell, all of which require inactivation to kill the cell. Surviving fraction of a cell population is given by the formula $SF = 1 - [1 - \exp(-D/D_0)]^n$.

Necrosis

Cell death associated with loss of cellular membrane integrity. Occurs in anoxic areas of tumours and is also a cause of cell death after irradiation.

Neurovascular syndrome

Total-body exposures of 10–20 Gy induce this syndrome within 1–72 h, leading to death within a few days. Early symptoms include nausea and vomiting. These and other symptoms, such as hypotension, fever, headache, neurological and cognitive deficits, and cardiovascular collapse, occur before the onset of toxicity in the gastrointestinal and haematopoietic systems.

Non-cancer diseases

Somatic diseases other than cancer (e.g. cardiovascular disease, cataracts).

Normal tissue complication probability

A term generally used in modelling normal tissue radiation response.

Occupational exposure

This refers to all exposure incurred by workers in the course of their work, with the exception of: (a) excluded exposure and exposure from exempt activities involving radiation or exempt sources; (b) any medical exposure; and (c) the normal local natural background radiation.

Oedema

Abnormal accumulation of fluid; for example, pulmonary oedema refers to a build up of fluid in the lungs.

Pericarditis

Inflammation of the pericardium, the membrane that surrounds the heart, most frequently attributable to infectious agents but also known to be caused by high doses of radiation.

Pharynx

Medical term for the throat from the nasal and oral cavities above to the larynx and oesophagus below.

Platelet-derived growth factor

A protein that induces growth of fibroblasts and is involved in wound healing. Also acts on some epithelial and endothelial cells, and on mesenchymal cells.

Poisson distribution

Distribution applicable when the probability of an event happening is small but the number of observations is large. The distribution of probabilities runs from zero to infinity, and an important characteristic of the distribution is that the mean equals the variance.

Prodromal phase

Signs and symptoms in the first 48 h following irradiation as part of the response to partial- or total-body irradiation ('radiation sickness').

Prognosis

The predicted or likely outcome.

Programmed cell death

Cell death that occurs as the result of an active process carried out by molecules in the cell. Examples include apoptosis, autophagy, senescence, and, in some cases, even necrosis.

Prophylaxis

Preventive measure or medication.

Protection quantities

Dose quantities that the Commission has developed for radiological protection that allow quantification of the extent of exposure of the human body to ionising radiation from both whole- and partial-body external irradiation and from intakes of radionuclides.

Public exposure

Exposure incurred by members of the public from radiation sources, excluding any occupational or medical exposure and the normal local natural background radiation.

Quasi-threshold dose

Dose point of extrapolation of the exponential portion of a multitarget survival curve back to the level of unity.

Radiation modifier

A substance (e.g. drug) which in itself does not evoke an effect on cells or tissues, but which changes the effect of radiation.

Radioresponsiveness

Rate of response of a tissue to irradiation. The clinical responsiveness to a course of radiation therapy. This depends on multiple factors, one of them hypothesised to be cellular radiosensitivity.

Radiosensitiser

In general, any agent that increases the sensitivity of cells to radiation. Commonly applied to electron-affinic chemicals that mimic oxygen in fixing free radical damage, although these should more correctly be referred to as 'hypoxic cell sensitisers'.

Radiosensitivity, cellular

The sensitivity of cells to ionising radiation in vitro. Usually indicated by the surviving fraction at 2 Gy (i.e. SF₂) or by the parameters of the linear-quadratic or multitarget equations.

Recovery

At the cellular level: an increase in cell survival as a function of time between dose fractions or during irradiation with low dose rates. At the tissue level: an increase in tissue iso-effective total dose with a decrease in dose per fraction or with irradiation at low dose rates.

Relative biological effectiveness

The ratio of a dose of a low-linear energy transfer reference radiation to a dose of the radiation considered that gives an identical biological effect. Values vary with the dose, dose rate, and biological endpoint considered.

Relative risk

An expression of risk relative to the underlying baseline risk. If the total risk is twice the underlying baseline risk, the relative risk is 2.

Repopulation

Describes the proliferation of surviving clonogenic tumour cells during fractionated radiotherapy. Rapid repopulation of clonogenic tumour cells during therapy is an important factor in treatment resistance. Also describes the regeneration response of early-reacting tissues to fractionated irradiation, which results in an increase in radiation tolerance with increasing overall treatment time.

Reproductive integrity

Ability of cells to divide many times and thus be 'clonogenic'.

Senescence

A permanent arrest of cell division associated with differentiation, ageing, or cellular damage.

Sievert (Sv)

The special name for the SI unit of equivalent dose, effective dose, and operational dose quantities in radiation protection. The unit is joule per kilogram (J/kg).

Doses in Gy are multiplied by a quality factor which depends on the particular detriment to obtain sieverts. The sievert should not be used in the quantification of radiation doses or in determining the need for any treatment in situations where tissue reactions are caused. In general, in such cases, doses should be given in terms of absorbed dose in gray (Gy), and if high-linear energy transfer radiations (e.g. neutrons or alpha particles) are involved, a relative-biological-effectiveness-weighted dose, $RBE \cdot D$ (Gy), may be used.

Slow repair

Long-term recovery that takes place on a time scale of weeks to months, often associated with long-term intracellular repair.

Stem cells

Cells with an unlimited proliferative capacity, capable of self-renewal and of differentiation to produce all the various types of cells in a lineage.

Stochastic effects of radiation

Malignant disease and heritable effects for which the probability of an effect occurring, but not its severity, is regarded as a function of dose without threshold.

Stroke

Interruption of the blood supply to the brain due to blockage or rupture of vessels. Loss of blood and oxygen to areas can lead to cell death and, consequently, permanent brain dysfunction. Two major forms of stroke are recognised: ischaemic stroke caused by blockage due to blood clots forming locally (thrombotic stroke), or fragments from distant clots lodging in the brain vasculature (embolic stroke).

Syndrome

A group of signs or symptoms that occur together and characterise a disease or abnormality.

Target cell

A (renewing) cell whose death contributes to a reduction in tissue function.

Telangiectasia

Pathologically dilated capillaries and very small arteries, observed in all irradiated tissues and organs in association with late radiation effects.

Threshold dose for tissue reactions

Dose estimated to result in only 1% incidence of defined tissue reactions.

Time factor

Describes the change in iso-effective total dose for local tumour control or normal tissue complications that follows a change in the overall treatment duration.

Tissue-rescuing unit

Unit of tissue capable of rescuing a tissue from failure.

Tolerance dose

The maximum radiation dose or intensity of fractionated radiotherapy that is associated with an acceptable low complication probability (usually 1–5%). Actual values depend on treatment protocol, irradiated volume, concomitant therapies, etc., but also on the status of the organ/patient.

Transforming growth factor

A cytokine that regulates many of the biological processes essential for embryo development and tissue homeostasis, and which therefore plays a role in tissue healing. The effects may differ depending on the tissue involved, e.g. transforming growth factor beta inhibits the proliferation of epithelial cells but stimulates proliferation of fibroblasts.

Transit cells

Differentiating proliferative cells that amplify cell production in a hierarchical tissue.

Volume effect

Dependence of radiation damage on the volume of tissue irradiated and the anatomical distribution of radiation dose to an organ.

Xerostomia

Dryness of the mouth caused by malfunctioning salivary glands.

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1. INTRODUCTION

1.1. Purpose of report

(6) The aim of this report is to review the tissue and health effects of ionising radiation, with particular reference to their implications for dose limits in radiation protection, and for assessing health risks after accidental or therapeutic exposure. The report was prepared by a Task Group of ICRP Committee 1 under the following terms of reference: to review and evaluate the literature on the non-cancerous effects of ionising radiation on normal tissues, both in the context of high doses received by cancer patients treated with radiotherapy or in accidents, and lower doses sustained during accidental or occupational exposures, or during other incidents of unknown magnitude. This report updates the information given in *Publication 41* (ICRP, 1984), including new data on cardiovascular effects and the risk of radiation-induced cataracts (Section 2). The influence of potential modifiers of the basic radiation sensitivity of normal tissues will also be considered with respect to compounds that either exacerbate and increase, or ameliorate and reduce, radiation injury (Section 3).

(7) This report deals with the above considerations but does not claim to represent an exhaustive literature review. Several extensive reviews have been published for radiation effects in normal tissues (Potten and Hendry, 1983; UNSCEAR, 1988; Scherer et al., 1991; AGIR, 2009; Shrieve and Loeffler, 2011), as well as for particular organ systems such as skin (Potten, 1985; ICRP, 1991), intestine (Potten and Hendry, 1995), bone marrow (Hendry and Lord, 1995), and the immune system (UNSCEAR, 2006). Instead, this report provides a critical evaluation of the radiation response of each of the various tissues for radiation protection purposes (Section 4), with special reference to those tissues and organs that are considered to be most important, based on analysis of the relevant human and laboratory data. The format for this report was chosen so that different aspects of the response of each organ system are described serially in Sections 2, 3, and 4. The detailed effects of high-linear energy transfer (LET) irradiation and prenatal irradiation are not included because they were dealt with in ICRP *Publications 58* (ICRP, 1990) and *90* (ICRP, 2003), respectively.

1.2. Definition and nature of tissue reactions to ionising radiation

(8) After high doses of radiation, there may be a substantial amount of cell killing, sufficient to result in detectable tissue reactions. These reactions may occur early (days) or late (months to years) after irradiation, depending on the tissue in question. The depletion of renewing parenchymal cell populations, modified by stromal influences, plays a crucial role in the pathogenesis of early tissue reactions. The dose at which damage is detected depends on the specified level of injury and the sensitivity of the method used to detect it.

(9) When the term 'stochastic' was introduced to describe single-cell effects, such as mutagenesis, effects caused by injury in populations of cells were called 'non-

stochastic' in *Publication 41* (ICRP, 1984). This was later considered to be an unsuitable term, and it was replaced with the term 'deterministic', meaning 'causally determined by preceding events', in *Publication 60* (ICRP, 1991). Now it is recognised that both early and late tissue reactions are not necessarily predetermined, and they can be altered after irradiation by the use of various biological response modifiers. Hence it is considered preferable to refer to these effects as early or late tissue or organ reactions. In *Publication 60* (ICRP, 1991), the emphasis was on radiation-induced cell killing in relation to tissue damage. It has since become clear that the cytotoxic effects of radiation cannot explain all tissue reactions, and that non-lethal effects of radiation on cells and tissues, with the resultant disturbances in molecular cell signalling, also play a crucial role in determining tissue response to radiation. This is further elucidated in Section 1.3.7.

(10) The manifestations of tissue injury vary from one tissue to another depending on cellular composition, proliferation rate, and mechanisms of response to radiation, which may be highly tissue specific. Examples, which are discussed in more detail in Section 2, include cataracts of the lens of the eye, non-malignant damage to the skin, cell depletion in the bone marrow causing haematological deficiencies, and gonadal cell damage leading to impairment of fertility. Tissue reactions, especially late reactions, also depend on damage to blood vessels or elements of the extracellular matrix, which are common to most organs of the body.

(11) Early tissue reactions (hours to a few weeks after irradiation) may be of an inflammatory nature, occurring as a result of changes in cell permeability and the release of inflammatory mediators. Subsequent reactions are often a consequence of cell loss (e.g. mucositis and desquamation in epithelial tissues), although non-cytotoxic effects on tissues also contribute to these early reactions. Late tissue reactions (months to years after irradiation) are called 'generic' if they occur as a result of injury directly in the target tissue (e.g. vascular occlusions leading to deep tissue necrosis after protracted irradiations), or 'consequential' if they occur as a result of severe early reactions (e.g. dermal necrosis as a result of extensive epidermal denudation or chronic infection, and intestinal strictures caused by severe mucosal ulceration) (Dorr and Hendry, 2001). However, it is important to realise that these two conditions are not mutually exclusive but often co-exist.

(12) It has been increasingly recognised that the structure of tissues and organs plays a major role in their response to irradiation. Paired organs (e.g. kidney and lung) or organs where the functional subunits (FSUs) are arranged in parallel (e.g. liver) can sustain inactivation of many FSUs without clinical signs of injury because of a substantial reserve capacity and compensation by the remaining FSUs. This is one of the major reasons for the presence of a threshold dose for functional injury, especially for increased tolerance to partial-organ irradiation, where a critical part of the organ may be spared. Above this threshold dose, increasing severity of functional impairment occurs with increasing dose. In contrast, organs with a serial structure (e.g. spinal cord) have little or no functional reserve, and the tolerance dose is much less dependent on the volume irradiated. In these organs, the functional damage seen

above the threshold dose tends to be binary in nature, rather than increasing in severity with dose (see Section 1.3.6).

(13) A threshold dose for a given effect can be defined as a dose below which the effect does not occur. This dose is often difficult to determine. One way in which epidemiological evidence for a threshold can be assessed is by examination of the lowest dose at which a significant positive dose–response relationship can be detected. This is subject to constraints on sample sizes and to the particular model used to fit the data. In this report, the ‘threshold dose’ is defined as ED_1 (estimated dose for 1% incidence), denoting the amount of radiation that is required to cause a specific, observable effect in only 1% of individuals exposed to radiation (ICRP, 2007: Annex A, Fig. 1.1). Although ED_1 is not a ‘true’ threshold in the sense of the effect not occurring at all, it is used here in a practical sense for protection purposes. The use of a smaller level than ED_1 would entail a greater extrapolation of response frequencies to even lower doses, with concomitant greater uncertainties attached to the value. The use of a higher level would have less uncertainties in the value, and this may be acceptable in practical situations for some endpoints but not others. However, it would be even further

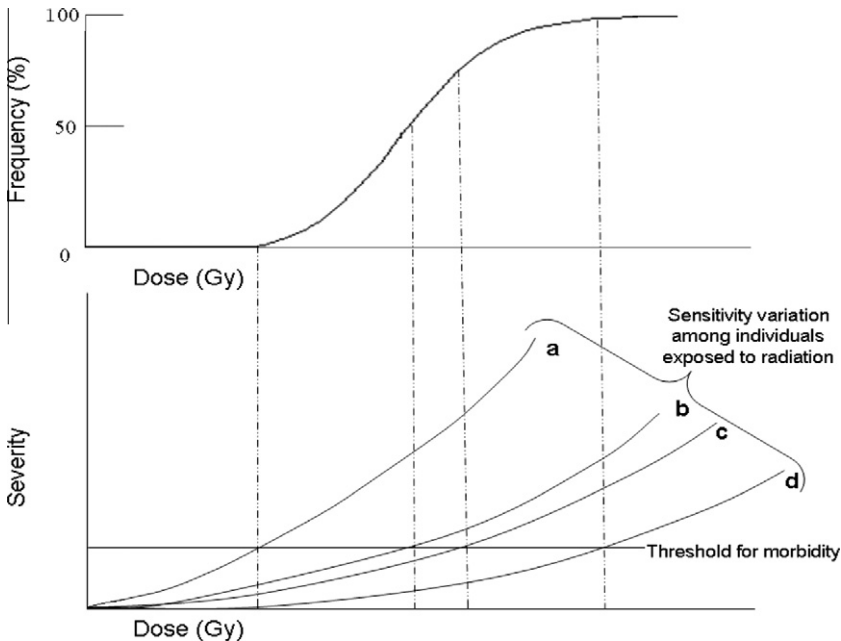


Fig. 1.1. Relationships between dose and the frequency or severity of tissue reactions. Upper panel: the incidence (frequency) of morbidity as a function of dose in a population of individuals of varying sensitivities. Lower panel: the dose vs reaction severity relationship for four subpopulations with different radiosensitivities (‘a’ being most radiosensitive, ‘d’ being least radiosensitive) comprising the total population. Adapted from *Publication 60* (ICRP, 1991; Hendry et al., 2006).

from the 'true' threshold. In the case of erythema of the skin, for example, ED_1 is approximately 5–6 Gy received in a single exposure, which is higher than ED_1 for temporary depilation (4 Gy) but lower than ED_1 for desquamation and necrosis (6–10 Gy), as discussed in Section 2.4. The definition of ED_1 may be complicated by substantial baseline levels of specific tissue effects or diseases that develop with ageing in the absence of radiation exposure (e.g. cataracts and circulatory disease). In all these cases, ED_1 refers to effects just starting to rise above the baseline levels in unirradiated, age-matched individuals and, in the case of circulatory disease, to a dose which would increase the already high natural incidence or mortality by only 1%. ED_1 does not imply that no biological effects occur at lower doses; it merely defines the dose above which a specified effect becomes clinically apparent in a small percentage of individuals.

(14) In contrast to ED_1 , the term 'tolerance dose' is used to denote the maximum amount of radiation that a tissue can withstand without developing clinical signs of injury in more than a few percent of individuals. The term 'clinically significant' is used to denote the level of severity that is not only detectable but is associated with noticeable symptoms or signs of impairment of function. The available knowledge on dose–effect relationships for tissue or organ reactions in man derives largely from radiotherapeutic experience, delineating the doses and conditions of radiation that do or do not cause adverse side-effects in a small percentage of patients. The criterion is often taken at the level of 1–2%, but it varies depending on the severity of the injury. It will be <1% in the case of induced paralysis, whereas it may be a few percent in the case of other less severe and treatable injuries. The scoring of such effects has, however, usually relied on relatively crude measures of severity (i.e. gross clinical manifestation). Hence, the term 'tolerance' as used in this report denotes the capacity of a tissue to withstand irradiation without evidence of the detrimental effect in question. It does not imply that less severe effects (i.e. subclinical) are absent. Also, it should be recognised that the majority of late radiation effects progress with time. Tolerance doses, for a specific level of damage, are therefore not absolute but they decrease with increasing follow-up time, and they should be quoted as pertaining to a specified time after exposure (e.g. 5 years). A review of many different clinical data sets demonstrated that the development of the incidence of late normal tissue injury occurs with approximately exponential kinetics that could be quantified as the percentage of patients at risk of developing a specific effect per year (Jung et al., 2001). This percentage risk remained relatively constant with time for a specific late effect but varied between tissues (e.g. 5% per year for dermis and 12–14% per year for bladder and ileum) after pre-operative radiotherapy for rectal cancer (Jung et al., 2001). Most of the data reviewed continued annually for up to 10 years follow-up, but some studies showed the continuing expression of late injury for 20, 25, and 30 years for some tissues. This indicates that for protection purposes of workers and the public, very long follow-up times are needed to assess the accumulated expression of injury over a lifetime.

1.3. General principles of radiation effects in cells and tissues

1.3.1. Cell survival

(15) Cell depletion plays a major role in the early desquamatory reactions in epithelial tissues after irradiation. In a few cell types and tissues, rapid cell loss after irradiation is mediated by apoptosis, as exemplified by lymphocytes and salivary gland acinar cells. In other tissues, cell death is mainly caused by reproductive failure of regenerative stem cells, which may undergo apoptosis before or after attempted mitoses, or proliferating transit (differentiating) cells. The majority of non-proliferating mature cell types do not die from irradiation, but from natural senescence. Premature senescence may contribute to some late effects of radiation.

(16) The term ‘cell survival’ in the context of this discussion is defined as the ability of a cell to proliferate indefinitely and to form a colony of daughter cells. The mean dose required to destroy a cell’s reproductive integrity is generally much less than that required to destroy its metabolic or functional activity. Thus, ‘cell death’ as used herein denotes the loss of the cell’s reproductive integrity, without necessarily the loss of its physical viability or other functions.

(17) For a given level of tissue damage in organs such as the intestine, a clear link has been shown between survival of tissue target cells and the level of early tissue damage, demonstrating the importance of target cell survival for these types of reaction (Thames and Hendry, 1987). For slowly developing late tissue reactions, the link between target cell survival and damage is much less clear.

(18) Since *Publication 60* (ICRP, 1991), there has been a consolidation of the use of the linear-quadratic (LQ) formalism for describing cell survival as a function of dose and comparing the changes in iso-effective total dose resulting from changes in the dose rate or size of the dose per fraction (Fig. 1.2).

(19) In the LQ formula: $S = \exp -(xD + \beta D^2)$, the constant α describes the linear component of cell sensitivity to killing on a semi-log plot of survival (log) vs dose

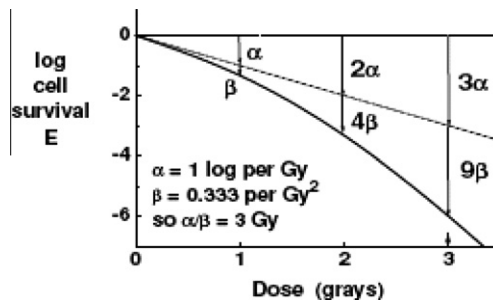


Fig. 1.2. Dose–response relationship for cell survival (S) on a semi-log plot of $(-\log S = E)$ vs dose, described by the linear-quadratic equation $S^0 = \exp -(xD + \beta D^2)$ or $E = (xD + \beta D^2)$ (Fowler, 2006). α and β are the coefficients of the non-repairable and repairable components of radiation damage, respectively. α is the number of logs (e) of cell kill per Gy, and β is the number of logs per Gy^2 . The β component fades with a half-time of minutes to hours; therefore, very low dose rates give survival curves close to the α curve.

(linear), and β describes the increasing sensitivity of cells to higher radiation doses. The ratio α/β is the dose at which the linear (non-repairable) and quadratic (repairable) components of cell killing are equal. This ratio is a measure of the curvature of the survival curve. The β component tends to be larger, and hence the α/β ratio is lower and the curve on a semi-log plot is more pronounced, for homogeneous, slowly proliferating cell populations, such as in slow-renewing organ systems (e.g. kidney and spinal cord). The β component is relatively less, and hence the α/β ratio is higher and the survival curve is straighter, for heterogeneous, rapidly proliferating cell populations (e.g. regenerative target cell populations in oral mucosa and intestine). One contributor to this straightening is the relatively short time available for repair between irradiation and mitosis. Another possible contributor is the presence of sub-populations with different sensitivities as a function of cell-cycle phase. The α/β ratio is generally in the range of 7–20 Gy for early reactions in tissues (10 Gy is commonly used as an average value) and 0.5–6 Gy for late reactions (3 Gy is commonly used as an average value). This application of the LQ model does not include a time factor, so no account is taken of repopulation of surviving cells with increasing total overall treatment time.

(20) The half-time for repair is generally 1–2 h, and there is often a second slower repair component. This means that after an acute exposure, it is many hours before the surviving cells have undergone near-complete repair. Incomplete repair becomes important when fractionated exposures are given (see below). When dose rates are lower than approximately 0.10 Gy/min, there is some repair of cellular radiation injury during the exposure. This causes the β component to decrease and to reach zero at very low dose rates. The α component is not modifiable by changing dose rate. A special feature for some cell types is hypersensitivity to doses of <0.5 Gy. In cells that exhibit this hypersensitivity, the shape of the radiation survival curve at low doses is characterised by a steeper slope than that expected by back-extrapolation of the response at higher doses. This is considered to be due to stimulation of repair processes at doses of >0.2–0.3 Gy, when sufficient DNA double-strand breaks are induced to trigger damage response signalling (Joiner et al., 2001). Hence, this is a limitation on the use of LQ methodology at these low doses. The phenomenon has been detected for early skin reactions in humans, and for skin reactions and kidney injury in experimental animal systems, as well as in vitro. The relevance of this hypersensitivity phenomenon for tissue injury thresholds is not yet clear. With high-LET irradiations, there is less repairable injury, and hence the β component and dose-rate effects are small or absent. There is also no hypersensitivity component to the survival curve after high-LET radiation.

(21) In the early days of radiobiology, the dose–response curve was described as having an initial shoulder, followed by a portion that is straight, or almost straight, on a semi-log plot. The curve was characterised by two of three parameters: D_0 , the dose required to reduce survival to 37% on the exponential part of the curve, and the extrapolation number n on the log-survival axis, or D_q (the quasi-threshold dose, the extrapolate of the exponential curve on the dose axis). The survival curve parameters were related by $\log_e n = D/D_0$. Now it is recognised that although the latter formalism is often a good representation of single-dose responses at high doses, the LQ

formalism is more appropriate for use in fractionated doses, as used clinically where the size of dose per fraction varies within quite a narrow range. This range is in the shoulder region of the cell survival curve, which is poorly described by D_0/n terminology.

1.3.2. Tissue kinetics

(22) Tissues vary widely in the rates at which their constituent cells are normally replaced, and in the population dynamics through which the production, differentiation, ageing, and loss of such cells occur. These differences affect the rapidity with which different tissues manifest the effects of irradiation, since the expression of radiation cell death is generally delayed until mitosis. Rapidly proliferating tissues have a defined stem cell compartment (capable of indefinite cell renewal), which gives rise to a proliferating cell compartment and compartments of differentiating and functioning postmitotic cells. The timing of radiation-induced injury depends on the life span of the mature cells, which are comparatively radioresistant, and it is thus relatively independent of dose. During fractionated or protracted exposures, proliferation of stem cells may compensate for cell killing and reduce the damage from irradiation. Examples of rapidly proliferating tissues include the epithelium of the intestinal mucosa, the bone marrow, and the epidermis.

(23) Other types of tissues may possess stem cells, but these do not operate in the same way as in clearly hierarchical tissues to rescue tissues from failure after acute doses. They also possess large populations of functional mature cells that are still capable of a few divisions to help in restoring function after some cell depletion. These tissues were called 'flexible tissues', and now are more commonly called 'complex tissues'. They generally have very low levels of cellular proliferative activity, and the timing of their response to radiation is dose-dependent but may not be evident until a long time after irradiation. Far less protection by regenerative or compensatory proliferation is to be expected during fractionated or protracted exposures in tissues of this type; for example, the liver where parenchymal cell renewal is low, or blood vessels where endothelial cell turnover is also very low (Michalowski, 1981; Wheldon et al., 1982).

(24) Since tissues and organs consist of a variety of cells with differing rates of proliferation, the expression of radiation injury does not occur at the same time in all cell population compartments within a given tissue. With fractionated or protracted exposure, the expression of radiation injury also tends to be complicated by compensatory proliferation and other homeostatic processes that alter cell kinetics.

(25) At the tissue level, a variety of mechanisms may lead to a threshold for impairment of tissue function, even if there is no threshold for the killing of target cells. These mechanisms include repopulation by surviving cells; the ability of differentiating, maturing, and functional cells to compensate to some extent for injury in the stem cell compartment; the capacity of the tissue to undergo compensatory changes to maintain its supply of differentiated cells; and functional reserve capacity in an organ. This may explain why relatively large doses are sometimes required to

produce a noticeable loss of tissue function, and why this threshold varies according to tissue and the functional parameter being considered.

1.3.3. Effects of fractionation and protracted irradiation

(26) When a dose of radiation is split into two or more fractions, its biological effectiveness is generally reduced. The two main factors contributing to this effect are repair of sublethal damage and replacement of lethally injured cells by repopulation. Other types of intracellular repair, potentially lethal damage and slow repair, may similarly contribute to an increase in survival. Cell replacement may also occur by migration of unirradiated cells from unaffected regions.

(27) As opposed to the effects of intracellular repair and cell replacement, reassortment of the cells in the surviving population into radiosensitive stages of the cell cycle may, under certain conditions, increase the cytotoxic effectiveness of a given dose when it is fractionated (Withers and Elkind, 1969; UNSCEAR, 1982).

Repair of sublethal damage

(28) Low-LET radiation is generally less effective per unit dose at low doses than at high doses, which indicates that cells can accumulate a certain amount of sublethal damage before losing their reproductive integrity. The extent to which repair of sublethal damage occurs is illustrated by the failure of successive doses to be fully additive in their lethal effects if separated by several hours; in other words, when a dose of low-LET radiation is delivered in two exposures, the dose required to kill a given percentage of cells increases as a function of time (up to several hours) between exposures. The repair potential of a tissue can be estimated from the value of the α/β ratio, which is a measure of the curvature of the target cell survival curve as well as an indication of the fractionation sensitivity of the tissue. The lower the α/β ratio for a tissue, the greater its potential for repair of sublethal injury.

(29) When the irradiation is given in many fractions, repair of sublethal injury occurs after each successive dose, and the multifraction survival curve is of the form shown in Fig. 1.3. When a dose is delivered in smaller increments, an increasing proportion of the lethal injury results from the initial non-repairable component of the damage. Ultimately, a dose per fraction (≤ 0.3 Gy/fraction for late reactions) or low dose rate (≤ 0.2 Gy/min) will be reached when all the sublethal damage is repaired, and only the initial lethal damage remains. In this case, the slope of the survival curve will be described solely by the α component (bold solid line in Fig. 1.4). There is also a 'reverse dose-rate effect' at a dose rate where cells accumulate in the radio-sensitive G2 phase of the cycle, and this sensitises the cell population slightly.

Repopulation

(30) Irradiation causes a dose-dependent period of mitotic delay, after which there may be renewed, or even accelerated, cell proliferation in rapid turnover tissues. With continuous irradiation at varying dose rates, the degree to which cell replacement is able to more than offset cell killing is indicated by the top line above the thick solid line in Fig. 1.4. The dose rate at which cell replacement can fully counterbal-

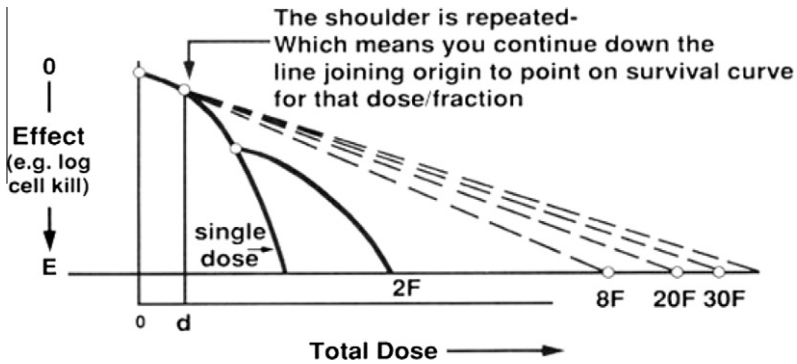


Fig. 1.3. The effective dose-response curve for a multifraction regimen approaches an exponential function of dose for many doses. The effective dose-response relationship is a straight line from the origin through the point on the single-dose survival curve corresponding to the daily dose fraction (typically 2 Gy) (Hall and Giaccia, 2006).

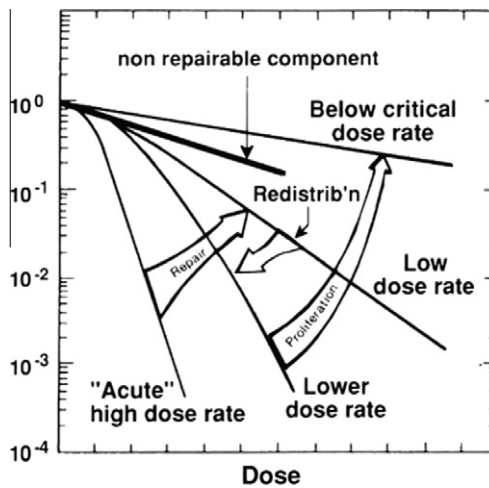


Fig. 1.4. The dose-rate effect resulting from repair of sublethal radiation damage, redistribution in the cycle, and cell proliferation. The dose-response curve for acute exposures is characterised by a broad initial shoulder. As the dose rate is reduced, the survival curve becomes progressively more shallow as more sublethal damage is repaired, but cells are 'frozen' in their positions in the cycle and do not progress. As the dose rate is lowered further, and for a limited range of dose rates, the survival curve steepens again because cells can progress through the cycle to pile up at a block in G_2 , a radiosensitive phase, but still cannot divide. A further lowering of dose rate below this critical dose rate allows cells to escape the G_2 block and divide; cell proliferation may then occur during the protracted exposure, and survival curves become shallower as cell birth from mitosis offsets cell killing from the irradiation (Hall and Giaccia, 2006).

ance cell loss varies markedly from one tissue to another, depending on the proliferative capacity of the cells in question. For the small intestine of the rat, in which the stem cells have an unusually high capacity for proliferation, the tissue is able to tolerate up to 4 Gy/day for a limited period of time (Quastler et al., 1959). In contrast,

the more slowly proliferating testis of the dog can tolerate only 0.0017–0.005 Gy/day when exposed daily for the lifetime of the animal (Casarett and Eddy, 1968; Fedorova and Markelov, 1978, 1979).

(31) For tissues with low rates of cell proliferation, repopulation does not occur until much longer after irradiation, and critical dose rates are not well understood. Failure to regenerate a tissue after irradiation may result in fibrosis and/or long-term loss of function in these tissues.

Chronic radiation exposures and effects

(32) Experimental animals and humans can tolerate higher total doses of chronic, low-dose-rate irradiation than acute single doses (Flidner et al., 2002). This is due to adaptive reactions at the cellular, organ, and whole-body level, in addition to repair of sublethal injury described above. The reaction of a tissue to low-dose chronic radiation exposure therefore reflects the simultaneous development of cell damage and adaptive processes (Rigaud and Moustacchi, 1996; Wolff, 1996).

(33) Radio-adaptation is defined as a modification of response to radiation exposure that makes it possible to maintain the individual's viability, fertility, and normal functional stability during chronic radiation exposure. Radiation adaptation manifests as increased radioresistance; therefore, the dose at which no damaging effects can be observed is significantly higher for chronic exposure than for acute exposure (Smirnova and Yonezawa, 2004). The induction of adaptive reactions decreases with increasing dose, and there is little effect above 0.5 Gy (Flidner et al., 2002). There is scant evidence on the effects of adaptation in case of exposures to high-LET radiation.

(34) There are two stages in the development of adaptation: the initial rapid but incomplete adaptation, followed by a persistent phase of adaptation. Rapid adaptation develops immediately after radiation exposure, and involves pre-existing physiological mechanisms, such as increases in the natural level of antioxidants. The persistent phase of adaptation develops gradually and involves mechanisms such as stimulation of DNA repair, induction of G₁ and G₂ checkpoints, induction of protein synthesis, stimulation of cell proliferation, and activation of radioprotective systems (e.g. endogenous stress proteins or antioxidants) (Nogami et al., 1993; Iku-shima et al., 1996; Seed et al., 2002). Glutathione produced in cells after exposure to small doses of radiation also has a stimulatory effect on immune reactions (Kojima et al., 2002).

(35) Chronic radiation syndrome (ChRS) is a clinical syndrome that develops in man after whole-body annual radiation exposures exceeding 0.7–1.0 Gy and cumulative doses exceeding 2–3 Gy over 2–3 years (Barabanova et al., 2007). ChRS is characterised by inhibition of haematopoiesis and immune reactions, and structural and functional disorders of the central nervous, cardiovascular, and other organ systems. The severity of these effects is determined by dose rate and total dose. The cessation of exposure to ionising radiation allows the occurrence of repair processes, which leads to rapid regression of the initial functional changes and slower normalisation of haematopoiesis. The rate and completeness of recovery depends on the extent of the tissue damage; it can be delayed for decades (Okladnikova et al., 1993, 1994; Akleyev and Kisselyov, 2002).

1.3.4. Iso-effect relationships

(36) Efforts to quantify the relationship between the severity of tissue damage, total dose, dose per exposure, number of exposures, and overall duration of exposure have led to various mathematical models or iso-effect formulae. These models have been useful in radiotherapeutic research and in clinical oncology. However, their relevance to radiation protection scenarios is limited since they may only apply at the level of maximal tissue tolerance, as judged by the absence of serious complications following radiation therapy, and they are not equally applicable to all tissues or all responses within a given tissue. Furthermore, extrapolation to highly fractionated or chronic exposures extending over many months or years is subject to considerable uncertainty. Nevertheless, these relationships may be of some value in estimating ED₁ doses for chronic exposures, as may occur after an accident.

(37) The most common approach is based on the survival curve model given by: $E = \alpha D + \beta D^2$, where E is a given effect from dose D . In this formula, the treatment time is not accounted for and must be allowed for separately. Since the contribution of the βD^2 term depends on interaction between intracellular sublesions, which must occur close to each other in space and time, it is strongly dependent on dose and dose rate. Hence, at very low doses and low dose rates, the response is determined by α , which is difficult to measure. Nevertheless, the ratio α/β is a useful parameter in describing the effects of fractionation and low dose rate, representing the dose at which the αD and βD^2 components contribute equally to the damage. The ratio α/β varies from approximately 1 Gy to 15 Gy, depending on the type of tissue and the particular response. In general, low values for α/β (below approximately 6 Gy, commonly 3 Gy is chosen as a generic value) apply to slowly proliferating tissues that give rise to late reactions. High values apply to rapidly proliferating tissues that give rise to early reactions (10 Gy is commonly chosen as a generic value) (Withers et al., 1980; Barendsen, 1982). The effect of incomplete repair can be allowed for by replacing βD^2 by $g\beta D^2$, where values of g are a function of both the time between fractions and the duration of continuous exposure (Thames and Hendry, 1987; Steel, 2002).

(38) The effects of increasing treatment time can be taken into account by allowing for the potential doubling time T_{pot} of a tissue after a lag period or 'kick-off time' T_{κ} :

$$E = nd(\alpha + \beta d) - (T - T_{\kappa})(\log_e 2)/T_{pot}$$

$$E/\alpha = nd(1 + d/(\alpha/\beta)) - (T - T_{\kappa})(\log_e 2)/(\alpha T_{pot})$$

where the biological equivalent dose is E/α , which is the equivalent total dose delivered at a very low dose rate, or using very many small fractions delivered at a high dose rate, i.e. $n \times d$ in the above formula minus the repopulation correction (Fowler, 1989). The actual repopulation correction, in terms of dose recovered per day due to proliferation, varies between renewal tissues and can be as high as 0.8 Gy/day for mucosa after a lag period of <12 days when using daily doses of 2 Gy (Bentzen and Baumann, 2002). However, it is near zero for virtually all late-reacting tissues, except where there is late consequential injury from early reactions (Dorr and Hendry, 2001).

(39) Another variant of this terminology is EQD2 (equivalent dose in 2-Gy fractions), where a dose per fraction of 2 Gy is used in the reference schedule. Biological equivalent dose or EQD2 are useful concepts because partial treatments can be added together, and EQD2 is particularly recognisable to most clinicians who are very used to treatments consisting of various numbers of 2-Gy fractions.

(40) As the above formulae were derived to relate different regimes in radiotherapy, they are reasonably accurate for therapeutic doses of irradiation lasting up to 6–7 weeks and doses per fraction of 1–8 Gy. With longer exposures, such as are of interest in radiation protection, extrapolation becomes increasingly uncertain.

(41) The effect of irradiating different volumes of tissue is not taken into account by the formula. In the simplest case, a doubling of the volume by a factor of 2 would double the number of target cells at risk in a tissue containing a homogeneous distribution of stem cells. However, the structural architectural arrangement of many organs makes the relationship between volume and response complicated (see Section 1.3.6).

1.3.5. Linear energy transfer

(42) With increasing LET, both the initial and final slopes of the dose–survival curve for irradiated cells become steeper (Fig. 1.5), accumulation of sublethal injury contributes relatively less to lethality, and repair of sublethal damage between fractional exposures is correspondingly reduced. Repair of potentially lethal damage and slow repair also decrease with increasing LET. As a result of each of these factors, the relative biological effectiveness (RBE) of high-LET radiation increases with decreasing dose or dose per fraction (Field and Hornsey, 1979) (Fig. 1.6), tending to become constant solely at low doses (<0.5 Gy) and low dose rates (<0.2 Gy/min) where only single-hit events are effective. These considerations also apply for carbon ions, which have about the same RBE as fast neutrons in the way that they are used clinically, but they have vastly superior depth-dose characteristics. In contrast to the repair of intracellular injury, which decreases with increasing LET, repopulation appears to be independent of LET (UNSCEAR, 1982).

(43) The increase in RBE with a decrease in dose per fraction is observed for tissues as well as for single cells. There is also a variation in RBE between tissues, depending on their repair capacity. These features of the increase of RBE with decreasing dose per fraction, the variation in RBE between tissues, and the higher RBE for late reactions (e.g. spinal cord, brain) vs early reactions in other tissues (e.g. haematopoietic tissue, skin) are shown in Fig. 1.7. These aspects and many other details of the RBE for tissue reactions (deterministic effects) have been described previously (ICRP, 1990).

1.3.6. Partial-organ irradiation

(44) The volume of a tissue irradiated to high therapeutic doses influences tolerance estimates. For an understanding of volume effects, it is important to distinguish

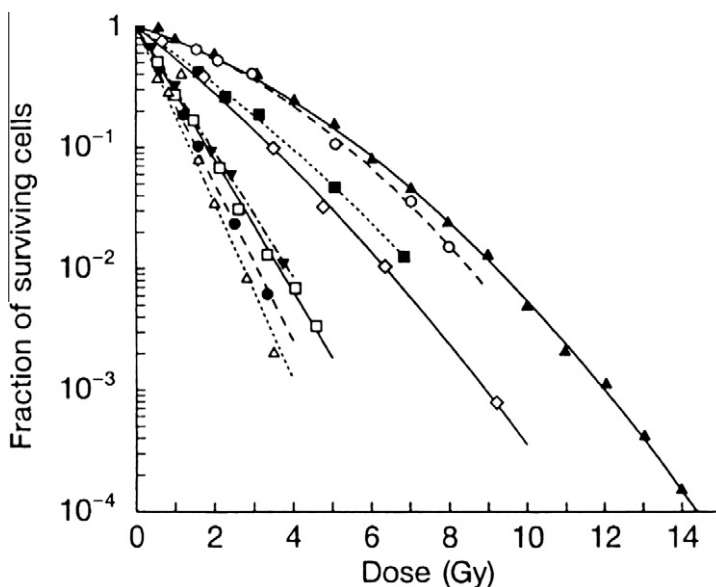


Fig. 1.5. Survival curves for human kidney cells exposed in vitro to 200 kV x rays (\blacktriangle) or radiation of increasing linear energy transfer (reproduced from Barendsen, 1968). \square , 2.5-MeV alpha particles, 165 keV/ μm ; \triangle , 4.0-MeV alpha particles, 110 keV/ μm ; \bullet , 5.1-MeV alpha particles, 88 keV/ μm ; \blacktriangledown , 8.3-MeV alpha particles, 61 keV/ μm ; \diamond , 26.0-MeV alpha particles, 25 keV/ μm ; \blacksquare , 3.0-MeV alpha deuterons, 20 keV/ μm ; \circ , 14.9-MeV alpha deuterons, 5.6 keV/ μm .

between the concept of structural tissue tolerance and clinical or functional tissue tolerance. Structural tolerance depends on radiation sensitivity per unit volume or area, and there is little evidence that this varies with the volume irradiated. However, the ability of an irradiated tissue or organ to maintain its function can vary considerably according to the irradiated volume and tissue architecture.

(45) Paired organs, such as kidneys or salivary glands, and organs in which the FSUs are arranged in parallel, such as lung and liver, have low tolerance to whole-organ irradiation, but small volumes can be irradiated to much higher doses without compromising total organ function. This is due to the considerable functional reserve capacity of such organs, where only approximately 30% of the organ is required to maintain adequate function under normal physiological conditions. In such tissues, there is a threshold volume below which functional damage will not develop, even after high doses. Above this threshold volume, damage is usually exhibited as a graded response (i.e. increasing severity of functional organ impairment with increasing dose rather than a binary, all-or-nothing response).

(46) In contrast, organs such as the spinal cord have a more serial organisation. In serially organised structures, the inactivation of one critical subunit may cause loss of function in the whole organ (Withers et al., 1988). Radiation damage in such tissues is expected to be binary, with a dose below which there is normal function and above which there is loss of function (e.g. radiation-induced myelopathy or small bowel obstruction). The probability of inactivation of any subunit with the same dose

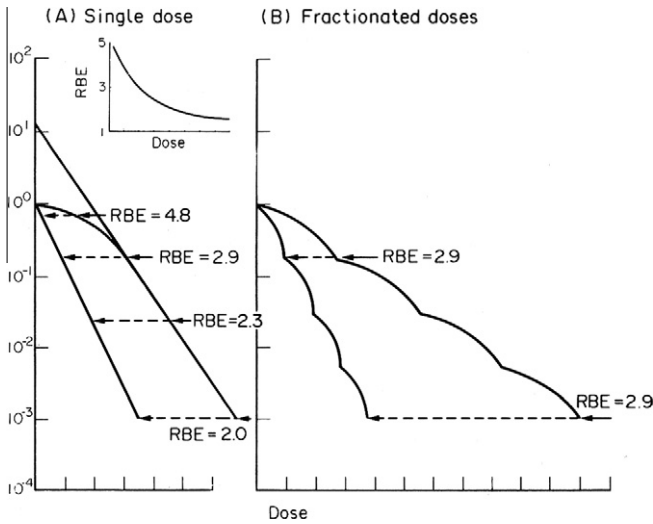


Fig. 1.6. Typical survival curves for mammalian cells exposed to x rays or fast neutrons. (A) Single doses. With x rays, the survival curve has a large initial shoulder; with fast neutrons, the initial shoulder is smaller and the final slope is steeper. As a result of the differences in shape, the relative biological effectiveness (RBE) is large for small doses, decreasing with increasing dose, as illustrated in the inset diagram. (B) Fractionated doses. The effect of giving four equal fractions of x rays or fast neutrons, each of which would give rise to an RBE of 2.9 (as illustrated in Panel A), is shown. Since the shoulder of each survival curve is expressed with each fractionated treatment (if sufficient time is allowed for full recovery of sublethal injury), the RBE for four fractions is the same as for a single treatment of the same dose per fraction. Thus, the curve relating RBE against dose, inset in Panel A, applies either to single doses or, in the case of fractionated treatments, to dose per fraction (ICRP, 1984).

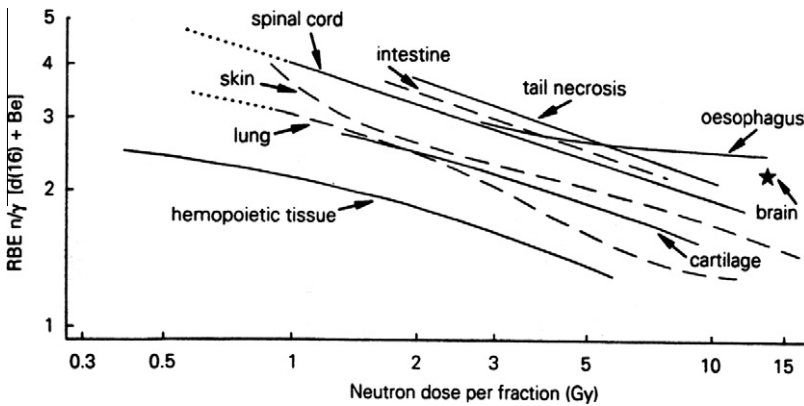


Fig. 1.7. Relative biological effectiveness (RBE) as a function of neutron dose per fraction for different normal tissues (Field and Hornsey, 1979).

of radiation increases with increasing length of the irradiated tissue. For these tissues, the risk of complication is strongly influenced by high-dose regions, even small hot spots of dose inhomogeneity.

(47) Several theoretical models have been developed to estimate normal tissue complication probability (NTCP) for partial volume irradiations and inhomogeneous dose distributions. These models reduce complex dose–volume distributions into a single dose parameter, and build mathematical descriptions for risk of damage. The models include at least two parameters, one describing the dose for a given probability of damage (e.g. 50%) and another describing the steepness of the dose–response relationship. Such modelling started with simple power law formulations (Lyman, 1985), and was followed by models with a more biophysical basis (Kutcher and Burman, 1989). Other models have attempted to include parameters relating to organisation of FSUs within a tissue, or their degree of ‘seriality’ (Withers et al., 1988; Kallman et al., 1992). In reality, however, organs are not organised simply as a chain of functional units, and purely serially organised tissues do not exist. In addition, the simple classification of serial and parallel organisation does not consider the influence of cellular migration and regeneration from outside the irradiated area, or regional differences in sensitivity within one organ, or the major contribution of damage from the supporting vascular networks in organs to the development of late radiation injury. Models for prediction of changes in tissue tolerance according to the volume irradiated should therefore be treated with caution. They should also be constantly re-evaluated using new clinical data emerging from dose escalation trials for intensity-modulated radiotherapy using reduced volumes of normal tissue in the high-dose region. Clinical data on partial-organ irradiation have been reviewed (Ten Haken, 2001; Marks et al., 2010).

1.3.7. Non-cytocidal radiation effects

(48) Radiation effects were classically described according to the target cell model, where the severity of injury and the time between irradiation and manifestation of injury depends on killing of target cells and their characteristics (radiation sensitivity, repair capacity, proliferation rate, etc.), and tissue organisation. However, it has now become clear that cell killing cannot explain all effects seen in irradiated tissues, especially late effects. In addition to damaging cellular DNA, reactive oxygen species (ROS) and reactive nitrogen species generated within irradiated tissues also alter proteins, lipids, carbohydrates, and other complex molecules, and initiate signalling pathways. Additional changes are elicited secondary to cell death. For example, fibrosis, which is a common late side-effect after radiotherapy, is caused by premature senescence and accelerated postmitotic differentiation leading to excessive collagen production by irradiated mesenchymal cells (fibroblasts, myofibroblasts, smooth muscle cells), not by cell kill. The paradigm for late radiation effects has now shifted from one based mainly on killing of target cells, to one based on an orchestrated tissue response involving release of cytokines and other mediators from damaged cells, leading to alterations in cell function as well as cell killing (Denham et al., 2001; Bentzen, 2006; Brush et al., 2007). These tissue responses (e.g. cytokine cascades) may be initiated well before significant cell killing and the manifestation of overt tissue damage, and they may persist for long periods. However, the mechanisms involved are not always fully understood.

(49) An additional characteristic of normal tissue toxicity in clinical radiation therapy relates to fractionation of dose. A series of insults is thereby delivered over a period of several weeks to tissues that undergo a dynamic spectrum of injury, repair, inflammation, and compensatory responses. Hence, during a course of fractionated radiation therapy, cellular and molecular responses will be exacerbated, suppressed, or altered, and the 'normal' tissue that is irradiated towards the end of a treatment course differs substantially from the normal tissue that was irradiated in the beginning (Denham and Hauer-Jensen, 2002).

(50) In summary, it is instructive to consider radiation responses of organs and tissues as the sum of three different injury processes that interact and together are responsible for the pathophysiological manifestations seen after radiation exposure: (a) cytotoxic radiation effects (target cell death by clonogenic cell death and/or apoptosis); (b) functional (non-cytotoxic) radiation effects; and (c) secondary (reactive) effects (Denham et al., 2001).

1.3.8. Heterogeneity in response

(51) There is heterogeneity in radiation response among individuals in a population. The cause is partly genetic, with different individuals having different gene expression profiles influencing response. Only very few individuals (much less than 1%) are homozygotes for mutations in critical repair genes and are consequently two- to three-fold more sensitive than the average person. The remainder are heterozygotes for these and many other relevant genes, having less contribution to radiosensitivity. The total population has a spread of sensitivities that governs the slope of dose–incidence curves for tissue or organ damage. In addition, there are epigenetic factors that result in comorbidities, such as the greater responses observed in individuals with human immunodeficiency virus. These effects are described in the sections for individual organ systems.

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2. RESPONSE OF TISSUES AND ORGANS TO RADIATION

2.1. Haematopoietic and immune systems

2.1.1. Anatomical features and proliferative organisation

(52) The haematopoietic system, structurally and functionally connected to the immune system, maintains a stable number of peripheral blood cells and immune homeostasis. The most important primary organs of the immune system are the bone marrow and thymus, along with secondary and tertiary lymphatic tissues. The haematopoietic stem cell (HSC) is central to the maintenance of steady-state haematopoiesis and thymopoiesis, as well as multilineage reconstitution after radiation-induced myelosuppression. Most HSCs are found in the bone marrow niche; however, they continue to migrate via the bloodstream throughout adulthood. The thymus, lymph nodes, spleen, tonsils, Peyer's patches, and solitary nodules of the mucous membranes make up the central and peripheral organs of the lymphoid system, all of which belong to the haematopoietic system. The thymus cannot support long-term progenitor self-renewal and is dependent on the immigration of bone-marrow-derived early T-cell progenitors and/or HSCs for continued production of new T cells.

(53) Haematopoiesis generates all blood cell lineages from privileged sites (niches) located within the bone marrow and thymus (Ladi et al., 2006; Scadden, 2006) (see Fig. 2.1). To maintain haemostasis, an adult produces approximately 2×10^{11} erythrocytes, 1×10^{11} leukocytes, and 1×10^{11} platelets each day. The haematopoietic tissue therefore produces approximately 4×10^{11} blood cells per day. This remarkable haematopoietic system is organised as a hierarchical progression of pluripotent and multipotent stem and progenitor cells that gradually lose one or more developmental options, becoming lineage-committed progenitor cells, which then continue differentiation into mature peripheral blood cells. HSCs are a small number of pluripotent, self-renewing, and largely quiescent cells that persist throughout life and dynamically regulate their numbers, although their turnover occurs over months to years (Chen, 2004; Sheperd et al., 2004).

(54) The stem cell niche provides a specialised setting of heterogeneous cells, tissue matrix, paracrine factors, and metabolic products that not only establish the three-dimensional (3D) niche, but also play essential roles in regulating adult stem cell survival, self-renewal, and differentiation. There is a complex interplay of humoral factors, cellular metabolism, and neurological stimuli (Arai et al., 2004; Fuchs et al., 2004; Zhu and Emerson, 2004; Ladi et al., 2006; Scadden, 2006). It is likely that vascular, perivascular, and endosteal cells contribute to specialised or common bone marrow niches near the endosteal surface. It is specific signals from certain niche sites that allow stem cell maintenance, renewal, and differentiation. Importantly, it is also the niche that provides the modulation in stem cell function needed under conditions of physiological challenge (Fuchs et al., 2004; Scadden, 2006). Although the vast majority of HSCs in the adult are located in the bone marrow, HSCs circu-

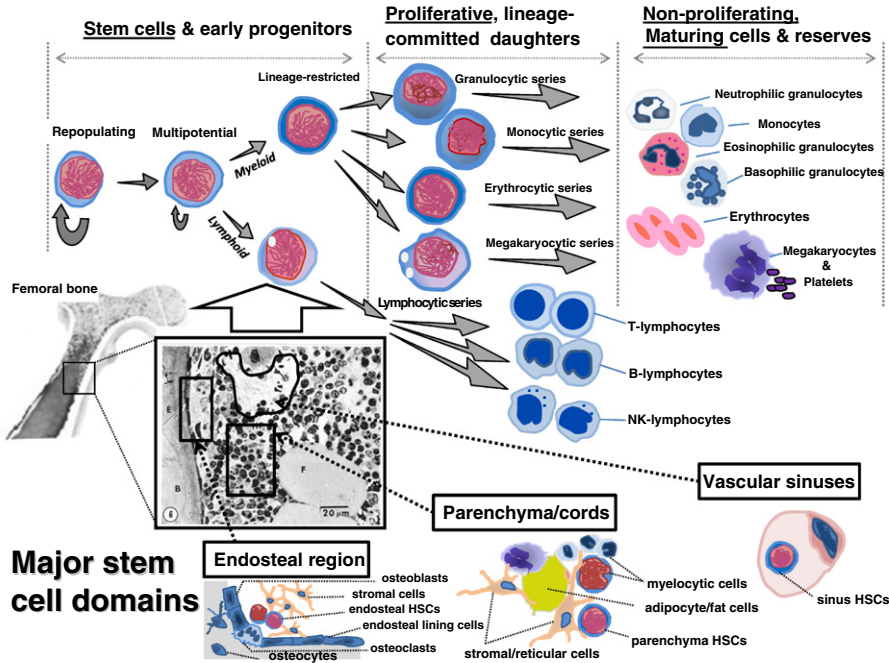


Fig. 2.1. General features of haematopoietic tissues. Their primary activity is the manufacture of various species of mature, functional cells that circulate in the blood. The bone marrow is an hierarchical, self-renewing, amplifying tissue, driven by small numbers of stem cells and early progenitors whose primary functions are to asymmetrically self-renew following rare divisional cycles, or to commit to differentiate into specific blood cell lineages. Stem cells and very early progenitors constitute the first of three major functional compartments within the bone marrow, while the second and third compartments are devoted to proliferative, lineage-committed progenitors, and to non-proliferating maturing cells and cellular reserves. Haematopoietic stem cells reside within three domains: (i) endosteal, (ii) parenchyma cord, and (iii) vascular sinus regions. The figure shown was conceptually derived from a National Institutes of Health online report (NIH, 2008) and modified by Dr. Tom Seed, Bethesda, MD, USA. NK, natural killer.

late freely, albeit at very low numbers. These HSCs, in response to specific stimuli, can exit and re-enter the endosteal and/or vascular niches via mobilisation and homing, respectively. The precise physiological roles of the circulating HSCs are unclear. They may provide a readily accessible source of HSCs and/or home back to the bone marrow niche and further influence HSC behaviour and physiological status. HSCs can regenerate the entire haematopoietic and immune systems, whether under homeostatic pressure or after cytotoxic chemotherapy or radiation. A fundamental question is how these niches affect maintenance and regeneration of HSCs and progenitor cells under steady-state conditions vs those after radiation-induced depletion.

(55) The bone marrow and thymus are the central haematopoietic and lymphoid tissues responsible for production of nearly all lymphocytes (UNSCEAR, 2006). All cells of the immune system originate from bone-marrow-derived HSCs. Sustained T

lymphopoiesis in postnatal life requires continued influx of thymus-seeding progenitors and/or HSCs from the marrow. The immature B cells and natural killer (NK) cells are produced within specialised niches within the bone marrow, whereas early thymic progenitors leave the bone marrow and migrate via the bloodstream to the thymus and initiate the complex production of naïve T cells. The thymus produces a variety of alternative T-cell subsets and lineages, including CD4+ and CD8+ T-cell subsets, regulatory T cells, gamma/delta T cells and NK T cells, with distinct effector activities and developmental pathways dependent upon specialised T-cell niches (Ladi et al., 2006). The first major revision of the Th1/Th2 hypothesis for T-cell-mediated tissue damage was proposed recently (Iwakura and Ishigame, 2006; Steinman, 2007). The new model is referred to as the 'Th17 hypothesis' and involves a complex interplay between the cytokine IL-23 and its induction of CD4+ T cells into IL-17-producing T helper cells. The Th17 cells also produce IL-6 and tumour necrosis factor (TNF) but not interferon- γ (IFN γ). It is very likely that the Th17 hypothesis will ultimately be refined to accommodate the increasing amount of information relative to the constellation of cytokines and T-cell subsets that produce and regulate recovery of tissue damage. The immune system is divided into primary, secondary, and tertiary organs (Picker and Butcher, 1992). The naïve T cells produced in the thymus recirculate via the blood into the secondary lymphoid organs (lymph nodes, spleen, Peyer's patches, etc.) where they can be activated by cognate antigen. Once activated, lymphocytes can enter tertiary, non-lymphoid sites, such as the skin and intestine, where they can participate in clearing infection. The small intestinal tertiary site is important in host defence, and its resident T cells are called 'intestinal epithelial lymphocytes'.

2.1.2. Acute radiation syndrome: haematopoietic effects

(56) Data generated from humans exposed to radiation, either during radiation therapy or as a result of accidents or nuclear weapons, have served as the source of information to determine the human radiation dose–response relationship and its modification by medical management and haematopoietic growth factors (HGFs) (UNSCEAR, 1988a; Anno et al., 1989, 2003; Hendry and Lord, 1995; Baranov et al., 1996; Waselenko et al., 2004). The data from available sources are listed in Table 2.1.

The LD_{50/60} for humans exposed to acute ionising radiation

(57) Lethality after total-body irradiation (TBI) is dependent on dose and dose rate. Reviews of the cumulative data on human radiation exposure suggest that the LD_{50/60} (50% lethality dose at relatively high exposure rates assessed 60 days after exposure) is approximately 3.3–4.5 Gy in the absence of medical management, and 6–7 Gy when medical management (consisting of antibiotics, blood products, fluids, antidiarrhoea compounds, nutrition, etc.) is provided (UNSCEAR, 1988b; Anno et al., 1989, 2003; Baranov et al., 1996; Waselenko et al., 2004). No HGFs were administered in these studies. A significant survival benefit of medical management has also been demonstrated in large animal models (Byron et al., 1964; MacVittie et al., 1991, 2005). In dogs, threshold doses can be approximately doubled

Table 2.1. Sources of information on the relationship between radiation dose and human lethality; medical management and haematopoieic growth factors.

Radiation source	Time/place	Number exposed/ estimated exposure	Treatments	References
15-kiloton nuclear device	Hiroshima, 1945	$n = 150,000$ casualties and 75,000 fatalities, all survivors <3 Gy	Medical management	Shimizu et al. (1992)
Nuclear reactor	Chernobyl, 1986	$n = 214$ with exposure $1-13$ Gy	Medical management	Baranov et al. (1996); Flidner et al. (1996); Georges and Storb (1997) Butturini et al. (1988)
^{137}Cs radiotherapy unit	Goiania, Brazil, 1987	$n = 10$, total-body doses of 2.5–7 Gy	GM-CSF Immunex, $500 \mu\text{g}/\text{m}^2/\text{day}$, i.v.	Rafael-Hurtado et al. (1996)
^{60}Co medical steriliser	San Salvador, 1989	$n = 3$, 3–10 Gy total-body doses with localised exposures (feet, legs) of 20 Gy in two workers	GM-CSF Leukine, $240 \mu\text{g}/\text{m}^2$, i.v.	IAEA (2000)
^{60}Co source	Istanbul, Turkey, 1998	$n = 10$, 0.7–4.0 Gy protracted doses	G-CSF Neupogen $5 \mu\text{g}/\text{m}^2/\text{day}$	Nagler et al. (1996)
^{60}Co from atomic reactor	Israel, 1990	$n = 1$, >10 Gy	IL-3 and GM-CSF after BMT	Baranov et al. (1994)
^{60}Co	Nyasvizh, Belarus, 1991	$n = 1$, 12–15 Gy	GM-CSF early (days 3–6) then IL-3 and GM-CSF (days 6–31)	Chiba et al. (2002); Nagayama et al. (2002)
Mixed neutron: γ radiation	Tokaimura, Japan, 1999	$n = 3$, 8–13 Gy	Stem cell transplant, G-CSF, erythropoietin, thrombopoietin	Liu et al. (2008)
^{60}Co source	Henan Province, China, 1999	$n = 3$, (a) 6.1 Gy (b) 3.4 Gy (c) 2.4 Gy	Medical management, antibiotics, transfusions, nutrition, GM-CSF ($50-400 \mu\text{g}/\text{m}^2/\text{day}$), and erythropoietin ($120 \text{ U}/\text{kg}/\text{day}$)	Zaharia et al. (2001)
^{192}Ir source	Yanango, Peru, 1999	$n = 1$, total-body doses of <3 Gy, 80 Gy to right thigh	G-CSF ($300 \mu\text{g}/\text{day}$)	Jinaratana et al. (2001)
Teletherapy head ^{60}Co	Samut Prakarn Province, Thailand, 2000	$n = 10$, ≥ 2 Gy (four received >6 Gy)	G-CSF Lenograstim, $10 \mu\text{g}/\text{kg}/\text{day}$ and GM-CSF $300 \mu\text{g}/\text{day}$	

GM-CSF, granulocyte-macrophage colony-stimulating factor; G-CSF, granulocyte colony-stimulating factor; BMT, bone marrow transplantation; IL-3, interleukin-3; i.v., intravenous. Note: In all of the above, where colony-stimulating factors were administered, medical management was also provided.

by the use of good clinical support and growth factors (MacVittie et al., 1991), demonstrating the potential of these approaches for exposed humans. A significant survival benefit of medical management was also considered a feature in the pre-Chernobyl and Chernobyl human experience (Baranov and Guskova, 1990; Baranov et al., 1996). These responses emphasise the value of medical management as the standard of care for severely irradiated personnel.

Summary of anecdotal data

(58) Medical management is an essential component of successful recovery from the haematopoietic syndrome following potentially lethal radiation exposure. The potential for spontaneous haematopoietic regeneration is always possible due to the likely non-uniform, inhomogeneous radiation exposure. HGF administration to victims of radiation accidents can result in positive benefit, but the marked inhomogeneity and uncontrolled nature of the radiation exposure and the insufficient numbers of people available for analysis prevent well-defined estimates of survival benefit and effect on the LD_{50/60}. The combined presence of other non-haematopoietic sequelae may complicate the treatment paradigm and worsen the potential for survival.

Pathophysiology of lethal radiation exposure

(59) A single, lethal radiation exposure of animals and humans leads to the acute radiation syndrome (ARS) (Baranov et al., 1988; Anno et al., 1989). The haematopoietic system is the organ system that is most sensitive in the ARS. Clinically recognisable signs of the haematopoietic syndrome can be observed after radiation exposures of 2–10 Gy. Radiation-induced myelosuppression results in a transient or prolonged period of neutropenia, thrombocytopenia, and lymphopenia as a consequence of a dose-dependent level of killing of HSCs and progenitor cells, and apoptosis (acute cell death) in the case of some types of lymphocytes. The recovery of a self-restricted, diverse T-cell repertoire is dependent on T lymphopoiesis consequent to recovery of haematopoietic HSCs and seeding of a competent thymus.

(60) After lethal irradiation, the haematopoietic syndrome is characterised by severe lymphopenia within 24–48 h. The rapid kinetics of lymphocyte depletion have been used to estimate exposure levels (Baranov et al., 1988; Flidner, 1988). Neutropenia and thrombocytopenia follow with varying onset times, depending on exposure dose and the circulating half-life of neutrophils and platelets. The kinetics associated with neutrophil loss have also been considered a reliable dosimeter (Baranov et al., 1988; Gusev et al., 2001).

(61) In the setting of neutropenia and thrombocytopenia, death from infectious complications and haemorrhagic events generally occurs within 14–28 days of irradiation. Treatment efficacy in terms of survival is dependent on protecting and/or enhancing recovery of the HSCs and progenitor cells, so that production of mature, functional neutrophils and platelets occurs within a critical, clinically manageable period of time. If the individual survives this critical period of myelosuppression, and only the haematopoietic subsyndrome is evident, recovery is likely. It is,

however, probable that after high-dose total-body exposure, a multiple organ syndrome may be evident (Azizova et al., 2005; Fliedner and Meineke, 2005).

(62) Immune suppression is also a common problem consequent to high-dose TBI similar to that noted with multicycle chemotherapy or myeloablative conditioning prior to stem cell transplant. The significant delay, for up to 1 year, in regeneration of naïve T cells, the limited T-cell repertoire, and compromised formation of the functional dendritic cell and T-cell axis leaves the patient at risk for infectious complications.

Medical management in acute radiation syndrome

(63) The most extensive experience on the use of medical management for ARS is derived from Chernobyl and other accident cases treated by the Clinical Department, Institute of Biophysics in Moscow, and entered in the computer database created in collaboration with the Department of Clinical Physiology, Occupational and Social Medicine, University of Ulm, Germany. These studies clearly emphasised the positive role of medical management in patients with severe ARS, and the minimal role to be played by bone marrow transplantation (BMT) or stem cell transplantation (Baranov et al., 1988; Fliedner et al., 1996; Densow et al., 1997; Georges and Storb, 1997). This database provides information on the response of humans to potentially lethal doses of TBI that is critical to the understanding of treatment in accidental exposure to radiation.

(64) It has been suggested that the most relevant parameter correlating with radiation dose causing severe ARS, after relatively uniform TBI, is the day on which the peripheral blood absolute neutrophil count (ANC) decreased to 500/ μl (d500) (Baranov et al., 1988; Baranov et al., 1996). If the patient had a d500 ≤ 14 , this corresponded to a total-body exposure of 5–6 Gy, leading to very severe myelosuppression. Before Chernobyl, only six known ARS patients with severe myelosuppression and medical management demonstrated immediate recovery of haematopoiesis. The d500 values for these patients were 9.5–14.0, which corresponded to uniform gamma irradiation doses of no more than 6–8 Gy. From 28 Chernobyl patients with very severe myelosuppression, 14 demonstrated spontaneous recovery of haematopoiesis. The recovery of these patients suggested that spontaneous regeneration of haematopoiesis could occur after TBI up to 8 Gy. Evaluation of neutrophil recovery curves from 18 patients who received estimated TBI doses of 4.7–8.3 Gy showed that ANC $< 100/\mu\text{l}$ was observed within 1–4 days of the respective d500 (Baranov et al., 1988; Baranov et al., 1996). Fever and infection coincided exactly with neutropenic periods after doses of 4–5 Gy, and these signs were more ‘aggressive’ in all patients after 5–6 Gy. These data underscore the need for prophylactic administration of antibiotics when the d500 estimates a relatively uniform lethal exposure, and ANC continues to decrease towards severe neutropenia when patients are at the highest risk of sepsis.

Lessons learned

(65) (a) The d500 correlates well with the dose of a relatively uniform TBI and indicates that the time to d500 for radiation exposure $\geq \text{LD}_{50/60}$ (6 Gy) is 9–14 days.

(b) All patients irradiated in the potentially lethal 4.7–8.3-Gy range experienced ANC <100 μ l within 1–4 days of the d500. (c) Spontaneous haematopoietic regeneration is possible from high lethal doses of suspected TBI in the accident scenario. It is likely that these individuals had non-uniform exposures with bone marrow sparing. (d) No HGFs were administered to these patients, emphasising the value of appropriate medical management in allowing sufficient time for recovery of haematopoiesis to occur spontaneously. (e) Bone marrow is noted for its small fractionation effect, but protraction of dose delivery allows marked repopulation. A summary of small numbers of individuals exposed to protracted doses in various accidents with minimal medical attention showed survival, at least in the short term, after estimated marrow doses of 10–14 Gy accumulated between 1 and 3 months (UNSCEAR, 1988a). Several models and formulae were proposed for describing the change in tolerance dose with increased fractionation and protraction of the irradiation, but human data remain scarce.

2.1.3. Haematopoietic effects of chronic exposure

Clinical data

(66) The haematopoietic system is characterised by high plasticity and good adaptability to chronic radiation exposure. This has been well documented both experimentally and in humans (Akleyev et al., 2002; Gidali, 2002; Guskova et al., 2002; Okladnikova et al., 2002; Seed et al., 2002). The human experience is illustrated in data from long-term follow-up of the Mayak facility workforce. Healthy young men exposed to external gamma radiation at dose rates of <0.25 Gy/year and cumulative doses from 1.0 to 1.5 Gy showed no evidence of reduced haematopoiesis. Higher annual doses of 0.25–0.5 Gy and total doses of 1.5–2.0 Gy led to cases of thrombocytopenia and unstable leukopenia. The highest total doses of 2–9 Gy resulted in leukocyte and thrombocyte counts of 50–65% of the baseline level. Some of these workers were also exposed to ²³⁹Pu aerosols, giving estimated absorbed doses to the red bone marrow of \leq 0.45 Gy. Reduced lymphocyte counts were noted at annual doses of >2.0 Gy and cumulative doses of >6.0 Gy (Pesternikova and Okladnikova, 2003).

(67) Termination of exposure was followed by gradual normalisation of leukocyte counts to 80–85% of baseline by the fifth year and to 88–95% by the 20th–25th year. However, even 40 years after exposure, leukocyte counts were still only 88–95% of the baseline level. Leukopenia at 40 years after exposure was more prevalent after cumulative red bone marrow doses of >2.0 Gy. Five years after termination of exposure to radiation, platelet counts were restored to normal in workers with cumulative doses of <6.0 Gy. For workers with higher cumulative doses, normalisation of platelet counts took up to 10 years (Pesternikova and Okladnikova, 2003).

(68) At 35–40 years after exposure to cumulative doses of 2–9 Gy (annual doses of >1.0 Gy), moderate bone marrow hypoplasia was still seen in 7% of Mayak workers (Okladnikova and Guskovava, 2001). Adaptive reactions in people with normal bone marrow cellularity manifest as increased erythropoiesis (13% of cases) and

increased proportion of proliferating granulocytes (18% of cases). The most significant reduction in bone marrow cellularity was noted at dose rates >2 Gy/year, although no dose dependency was seen for bone marrow hypoplasia at later times. The residual bone marrow hypoplasia and granulocytopenia was probably due to depletion of the stem and/or progenitor cell pools. Most of the workers with granulocytic hypoplasia had significant ^{239}Pu body burdens (Pesternikova and Okladnikova, 2004).

(69) Persistent reductions in platelet and leukocyte counts were also registered in Techa riverside residents, exposed for many years to combined external gamma and internal radiation, mainly ^{90}Sr , at bone marrow dose rates of >0.3 – 0.5 Gy/year (Akl-eyev et al., 1999; Akleyev and Kisselyov, 2002; Akleyev and Varfolomeyeva, 2007).

Experimental animal studies

(70) Animal studies have shown that the haematopoietic system is capable of maintaining an adequate number of cells during chronic low-dose and low-dose-rate radiation exposure. This is due to increased rates of cell production resulting from shortening of the cell cycle and maturation time (Grigoryev et al., 1986; Gidali, 2002), increased proliferative activity of stem cells and precursor cells (Muksinova and Mushkachyova, 1990), and stimulation of haematopoiesis (Lord, 1965; Flidner et al., 2002). Increased repair of sublethal lesions also occurs in bone marrow precursor cells (Seed et al., 2002).

(71) Experiments in dogs show that a dose rate of 0.075 Gy/day represents a threshold below which the blood-forming system retains its capacity for cell production for at least 1 year (Seed et al., 2002). At doses of >0.075 Gy/day, nearly 60% of the irradiated dogs died from progressive aplastic anaemia in <300 days. The remaining dogs exhibited a remarkable adaptability to low-dose/low-dose-rate exposure. In the initial period (50–150 days), the animals showed a progressive decline in bone marrow precursor cells, leukocytes, and thrombocytes in the circulating blood (Seed et al., 1980; Seed and Kaspar, 1992). This depletion subsequently slowed so that low, but functional, levels of bone marrow and blood cell reserves were maintained, with partial recovery at longer times. Leukocyte and thrombocyte counts decreased almost linearly with dose, without a threshold, whereas erythrocytes exhibited a non-linear response with a rather broad threshold (Seed et al., 2002).

(72) Chronic irradiation of dogs to doses of 0.62–1.9 Gy/year demonstrated the reversibility of haematopoietic changes resulting from long-term (3 years) exposure. Under conditions of chronic exposure, maintenance of erythroid cell homeostasis is a priority. The erythroid cell population is maintained at the highest level compared with other cell populations, and restoration of haematopoiesis also starts with normalisation of this cell series. On termination of chronic exposure, cell differentiation switches from preferential production of erythrocytes to production of granulocytes (Gorizontov et al., 1983).

(73) Rats and mice exposed to long-term irradiation at doses of 0.01–0.5 Gy/day (cumulative doses of 2–30 Gy) showed that the earliest and greatest depopulation occurred in the multipotent stem cell compartment [spleen colony-forming units (CFU-S)], which led to depletion of committed precursor cells and then of the functional

cell pool (Muksinova and Mushkachyova, 1990). The rate of recovery of the stem and/or progenitor cell subsets depends on dose rate (Wu and Lajtha, 1975). Normalisation of proliferating, maturing, and functional pools to control levels, as well as the CFU-S population, is faster after higher daily doses than at low dose rates for comparable total doses (Muksinova and Mushkachyova, 1990). This is because cellular decay products stimulate production of haematopoietic factors such as erythropoietin, leukopoietin, and thrombopoietin, which stimulate haematopoiesis and contribute to accelerated differentiation of committed cells and proliferation of stem and progenitor cells (Kaspar and Seed, 1984).

(74) The key factor triggering haematopoietic recovery is depletion of the stem cell compartment. Recovery and restoration of haematopoiesis is possible if >2% of stem cells and precursor cells are intact and capable of replication and differentiation (Fliedner et al., 2002). Long-term exposure to radiation induces depletion of the stem cell compartment and increases proliferative activity of these cells. Experiments in rodents show that increased proliferative activity of multipotent CFU-S occurs after exposure doses of 0.2–0.3 Gy; this leads to increased numbers of committed precursor cells and differentiated cells. Chronic exposures also stimulate proliferative activity in the committed precursor cells (Muksinova and Mushkachyova, 1990).

(75) The haematopoietic micro-environment, which normally maintains homeostasis of the stem cell pool by interaction with stem cells and multipotent progenitor cells (CFU-S), plays an important role in recovery after damage (Molineux et al., 1987; Muksinova and Mushkachyova, 1990). Extramedullary haematopoiesis and migration of HSCs from bone marrow to the spleen, liver, and lymph nodes can also occur. Recovery of haematopoiesis is more complete after exposure at low dose rates than at high dose rates. For example, in mice, recovery of haematopoietic and stromal progenitor cells was almost complete by 1 year after 12.5 Gy delivered at 0.0005 Gy/min compared with incomplete recovery after only 6.5 Gy given at 0.7 Gy/min (Gallini et al., 1988). Nonetheless, in other studies after low-dose-rate exposure, CFU-S were not restored to baseline levels during the lifetime of the animals, demonstrating some long-term residual injury (Muksinova and Mushkachyova, 1990). Under chronic exposure, bone marrow can be gradually replaced by fibrous tissue, which contributes to failure of bone marrow function (Seed et al., 1982; Fliedner et al., 2002). Immune and vascular disorders play an important role in this fibrotic development (Wynn, 2008).

(76) Lifetime exposure of rats to internal irradiation with ^{90}Sr , at daily intakes of 37 kBq and higher, resulted in a progressive reduction in circulating leukocytes. Reduced numbers of erythrocytes were only seen in animals with daily intakes of >185 kBq/day. The haemoglobin level was within normal limits over the entire experiment. However, animals given doses of 37 kBq/day had reduced bone marrow cellularity (30–80% of normal). The initial reduction in bone marrow cellularity was the result of a decrease in the erythroid cells and, at higher doses, a reduction in granulocytes (Shvedov and Akleyev, 2001).

Chronic radiation syndrome

(77) Cases of ChRS have been diagnosed in people chronically exposed to annual doses of 0.7–1.0 Gy and cumulative doses of >2–3 Gy (Barabanova et al., 2007). ChRS is slow to develop, with a latency inversely related to the dose rate of the exposure; ChRS develops over 1–3 years at annual exposure doses of 2–2.5 Gy, while the latency period may increase to 5–10 years at lower dose rates (Okladnikova, 2001).

(78) The first clinical sign of ChRS is a deficiency in haematopoiesis, which predominantly manifests as reductions in blood leukocyte and platelet counts and bone marrow hypoplasia (Guskova and Baysogolov, 1971). Initially, the number of leukocytes is typically reduced to 40–65% and the number of platelets is reduced to 50–60% of the baseline level (Okladnikova et al., 2002). Leukopenia is generally associated with a reduced number of granulocytes, while the lymphocyte count is less affected. Reduced blood lymphocyte counts observed after high doses (>4 Gy) usually lead to pronounced persistent leukopenia.

(79) In mild cases of ChRS, bone marrow changes involve a delay in the maturation of myeloid cells, sometimes in combination with an increase in reticular and plasmacytic elements. In more severe cases, bone marrow hypoplasia is seen (Akleyev and Kisselyov, 2002). Lethal bone marrow hypoplasia, resulting from irreplaceable loss of stem cells, is observed after exposure to dose rates of >4.5 Gy/year and total doses of >8 Gy (Guskova et al., 2002).

(80) Haematopoietic changes seen in ChRS are usually accompanied by changes in the immune, nervous, cardiovascular, and musculoskeletal systems, and in the gastrointestinal tract. Reduced resistance to infection and allergic changes in the organism are characteristic of the development of ChRS (Akleyev et al., 1995). Changes observed in the nervous system initially include vegetative dysfunction and asthenic syndromes. After high doses (4.5 Gy), encephalomyelitis-type changes may occur in the nervous system. This is due to focal demyelination, frequently of a transient nature, which appears to be dependent on vascular damage and certain metabolic disorders (Guskova, 2000; Guskova et al., 2002). ChRS may also manifest as dysfunction in other organs (e.g. reduced secretory function of the gastric mucosa, mild thyroid dysfunction, arterial hypotonia, and metabolic changes in the myocardium). These changes are probably the result of vegetative nervous system dysfunction.

2.1.4. Immune responses to chronic exposure

(81) A detailed description of radiation effects on the immune system has been published by UNSCEAR (2006). Variability in the immune response to radiation exposure may reflect differences in total dose and exposure uniformity (exposure dose to the thymus and bone marrow), dose rate, postexposure time, and age of the patient. However, there are data suggestive of the high dependence of radiation-induced immune changes on total dose but not on dose rate (Pecaut et al., 2001).

(82) Immunosuppression occurs after whole-body chronic irradiation at high doses, and it may be observed a long time after irradiation (Kirillova et al., 1988;

Okladnikova, 2001; Pecaute et al., 2001). Localised doses can also result in systemic immunosuppression. The mechanisms involved include: radiation-induced apoptosis of immunocompetent and progenitor cells, a shift in homeostatic balance between Th1 pattern (cell-mediated immunity) and Th2 pattern (humoral immunity) towards a pro-inflammatory profile, radiation-induced mutations in *TCR* genes, bystander effects, and genomic instability. Ionising radiation can also contribute to disturbing self-tolerance and pave the way towards autoimmunity. A key mechanism in the inhibition of the majority of immune parameters is apoptosis of circulating white cells, especially radiosensitive lymphocytes (Yagunov et al., 1998; UNSCEAR, 2006). Long-term recovery of a functional immune system depends upon concurrent recovery of the marrow-derived HSCs that serve as the source of early thymic progenitors (Guidos, 2006; Schwarz and Bhandoola, 2006).

(83) The radiosensitivity of immunocompetent cells depends on cell type, activation status, degree of differentiation, and in-vivo or in-vitro irradiation. B cells (CD19+) seem to be more radiosensitive subsets, both in vivo and in vitro, than CD4+ and CD8+ T cells, while NK cells are relatively resistant in vivo. Most of the data show no differences in radiosensitivity between CD4+ and CD8+ T lymphocytes. When activated by mitogens and antigens, T lymphocytes are more resistant than when not activated (UNSCEAR, 2006).

(84) In contrast, some animal studies indicate that low doses may enhance immune responses. Enhancement of the proliferative response of splenic and thymic lymphocytes to mitogens, enhancement of NK activity, and increased secretion of regulatory cytokines have been reported after doses of <0.05 Gy (Malyzhev et al., 1993; Safwat, 2000; Pandey et al., 2005). Evidence for similar effects on the human immune system is scarce. Data from animal experiments have shown that low-dose TBI could enhance the immune response through: augmenting the proliferative response of T lymphocytes to mitogenic stimulation, altering cytokine production [particularly IFN γ , INF γ , and interleukin-2 (IL-2)], increasing the expression of IL-2 receptors on the T-cell surface, facilitating signal transduction in T lymphocytes, increasing splenic catecholamine content and lowering the serum corticosterone level, eliminating a radiosensitive subset of suppressor T cells (Safwat, 2000), and modulation of oxidative status of immunocompetent cells (Kojima et al., 2002).

(85) Immune responses to radiation are genetically determined and dependent on the high polymorphism of the main histocompatibility complex (HLA in man, H2 in mouse) (Konenkov and Trufakin, 2002).

Innate immunity

(86) Although few data are available on the effects of low-dose exposure in humans, some data suggest that chronic exposure can induce an innate immune response. Several years after the onset of exposure to bone marrow doses of >0.3–0.4 Gy/year, residents of the Techa riverside villages demonstrated inhibited phagocytic activity of blood neutrophils, reduced circulating NK cell counts, and reduced lysozyme levels in their saliva (Akleyev and Kossenkov, 1991; Akleyev and Kisselyov, 2002). Reduced levels of the C3 and C4 components of the complements were also

seen in radiology workers exposed for a period of >5 years at dose rates of <0.0035 Sv/year (see note about units in Executive Summary) (Godekmerdan et al., 2004). Eight years after the accident at the Chernobyl nuclear power station, residents of contaminated areas exhibited decreased levels of NK cells, and clean-up workers exposed to doses of 0.1–3 Sv developed a dose-dependent reduction in the synthesis of leukocytic IFN and the C3 component of the complement (Semenkov et al., 1997; Asfandiirarova et al., 1998). However, under occupational levels of low-dose/low-dose-rate exposure, no effects of irradiation on the levels of NK cells were observed (Tuschl et al., 1990).

(87) Experiments on rodents confirmed that innate immune factors may change considerably following chronic irradiation. Low doses (≤ 0.2 Gy) enhanced the phagocytic activity of macrophages (Pandey et al., 2005) and enhanced secretion of IL-12 by peritoneal macrophages in mice (Liu et al., 2003). NK cells are relatively radioresistant. Low-dose-rate gamma irradiation (0.1 Gy/year) of mice resulted in increased CD49+ NK cells in the spleen at 28 and 32 weeks, while no changes occurred in the activity of NK cells (Lacoste-Collin et al., 2007). Moreover, activity of NK splenocytes increased in whole-body gamma-irradiated mice (0.5 Gy) 2–6 h after irradiation due to induction of endogenous glutathione (Kojima et al., 2002).

Acquired immunity

(88) Prolonged exposure of humans, even at low doses, may induce a dose-dependent decrease in cellular immunity, changes in the subpopulation composition of circulating immunocompetent cells, and suppression of their functional activity. Long-term follow-up of the population living around Chernobyl provides evidence of persistent changes, predominantly in the thymus-dependent immune response (decreased T-lymphocyte counts, decreased thymuline levels, increased levels of antibodies to thymic epithelial cells) (Yarilin, 1996; Asfandiirarova et al., 1998; Vykhoanets et al., 2000). As in the atomic bomb survivors (Hayashi et al., 2003), a preferential CD4+ cell deficiency was observed many years after the Chernobyl accident. The proliferative response to mitogens was also altered. Dose-dependent reductions in CD4+ and HLA-DR+ lymphocytes, and the CD4+/CD8+ cell ratio were also obtained in the follow-up studies of people who had lived in radioactive buildings for 2–13 years at a mean chronic dose of 0.17 Sv (Chang et al., 1999). The dynamics of postirradiation recovery of CD4+ and CD8+ cells were different, suggesting that radiation may induce damage to the thymus, accelerating the natural ageing of the immune system by a progressive decline in thymic function (UNSCEAR, 2006).

(89) In Techa riverside populations chronically exposed to radiation, long-term immunity changes involved decreased expression of differentiating antigens of T lymphocytes, decreased functional activity, and signs of immunological imbalance (Akleyev et al., 1995; Akleyev and Kisselyov, 2002). Persistent functional insufficiency of cellular immunity was observed in Mayak workers, even 35–40 years after exposure to external whole-body gamma radiation at accumulated doses of >4 Gy (Okladnikova, 2001).

(90) Chronically exposed individuals have also been shown to have higher lymphocyte-induced IL-4 and IL-10 production, and lower IL-2 and INF γ production (Attar et al., 2007), as well as a significant increase in immunoglobulin E (Ghiassi-nejad et al., 2004), which is indicative of the prevalence of the humoral immune response over the cellular response. However, in occupationally exposed radiation workers, no change was seen in the number of circulating B cells (Rees et al., 2004). Moreover, there was a decrease in the level of immunoglobulins (IgA, IgG, IgM) (Godekmerdan et al., 2004).

(91) In addition, continuous low-dose gamma irradiation (0.10 Gy/year) reduced B-cell activity in mice (Courtade et al., 2001), and increased production of incomplete autoantibodies attached to erythrocytes, and antibodies to splenic and hepatic tissue antigens in dogs (Grigoryev et al., 1986). Studies in rodents under continuous exposure to gamma radiation at higher dose rates (0.1 Gy/day) have shown a reduction in the proportion and functional capacity of cells involved in the humoral response to thymus-dependent antigen (Kirillova et al., 1988), inhibition of mitogenic T-lymphocyte stimulation, and a reduction in lymphocytes in the spleen (Novosyolova and Safonova, 1994). Changes in the synthetic activity of thymocytes were associated with the cyclic recurrence of suppression and recovery processes in the thymus (Sergeyevich and Karnaukhova, 2002).

Immune reactions to internal irradiation

(92) Studies in rodents showed that internal irradiation with tritium led to more pronounced and prolonged immune depression than external gamma radiation at similar total doses, due to more severe damage to the lymphocyte precursors. Experiments using mice demonstrated that prolonged exposure to tritium at cumulative doses of 0.2–1.0 Gy (dose rates of 0.033–0.092 Gy/day) caused disturbances in humoral immunity at different phases of immunopoiesis (Smirnov et al., 1990). Even at 12 months after chronic irradiation with tritium oxide, there was incomplete recovery of both cellular and humoral immunity. Hypoplasia of the thymus and lymphatic nodes long after irradiation is more pronounced than that of bone marrow and spleen (Murzina and Muksinova, 1982). Reduced function of NK cells under internal irradiation with tritium results from damage to their precursors and from inhibition of the radiosensitive process of IL-2 synthesis, which not only maintains their activity but also induces their proliferation and differentiation (Kirillova, 1985).

(93) Long-lived osteotropic radionuclides, such as ^{239}Pu and ^{90}Sr , accumulating in the bone tissue exert a long-term influence on the bone marrow. In rats, cytotoxic activity of NK cells was reduced after intravenous injection of ^{239}Pu , and skeletal doses of >3 Gy and 14 Gy inhibited humoral immunity (Kirillova et al., 1991). Exposure of red bone marrow to ^{90}Sr at dose rates of >2.5 mGy/day (cumulative doses of 0.7–1.0 Gy) caused inhibition of blood neutrophil phagocytosis and impaired antibody production (Shvedov and Akleyev, 2001).

2.1.5. Summary

(94) HSCs and progenitor cells are the primary target of chronic low-dose and low-dose-rate irradiation. Radiation-induced depletion of the stem cell and progenitor cell subsets results in increased proliferative activity of these cells, increased rates of repair of sublethal lesions in bone marrow precursor cells, accelerated cycling of bone marrow precursors, shortening of the maturation time, and stimulation of haematopoiesis. Decreased viability of mature blood cells results from ineffective haematopoiesis, thus causing restriction of blood cell reserves. Disturbances in acquired immunity and continued production of naïve T cells are likely to be caused by the extreme radiosensitivity of lymphoid tissue and by limited recovery of the restricted marrow-derived thymopoietic progenitor cell pool. Postirradiation recovery is characterised by gradual reconstitution of peripheral blood and bone marrow patterns. Partial recovery of haematopoietic and marrow-derived lymphopoietic precursors may be a limiting factor in sustaining recovery of a functional immune system. The persistent inflammatory status induced by ionising radiation has been associated with impairment of the immune system and late effects (cancer and non-cancer diseases).

(95) Animal data involving low-dose irradiation reinforce some of the clinical results, such as gradual reconstitution of peripheral blood and bone marrow patterns with partial deficiency of haematopoietic and lymphopoietic precursors. This suggests that ineffective haematopoiesis could cause restriction of myeloid and lymphoid cell reserves, and consequent disturbances in cellular and humoral immunity. Enhancement of immunity may be observed following very-low-dose irradiation, and modulation of oxidative status seems to be involved in this effect.

2.2. Digestive system

2.2.1. Anatomical features and proliferative organisation

(96) The alimentary tract extends from the mouth to the anus. It comprises the upper aerodigestive tract (oral cavity and pharynx) and oesophagus, which are lined by stratified squamous epithelium; the gastrointestinal tract (stomach, duodenum, jejunum, ileum, colon, rectum), lined by a single-layered columnar epithelium; and the squamous epithelial-lined anal canal. The organs of the alimentary tract, while covered by epithelial cells, are composite tissues that contain a variety of stromal cells, a rich microvascular network, large numbers of immune cells, and an extensive network of intrinsic and extrinsic nerves. In fact, the intestine is the largest immunological organ and the second largest nervous system in the body. The mechanisms and pathophysiology of radiation injury in the various segments of the digestive tract are similar in many respects, but there are also important anatomical and physiological differences that result in unique features of their radiation responses and tolerance (ICRP, 2006).

(97) It was previously believed that the severity of radiation injury in the gastrointestinal tract depended solely on the extent of apoptotic or clonogenic stem/progenitor cell death. This view has been supplanted by the recognition that radiation-induced changes in cellular function and many secondary (reactive) processes contribute substantially to the pathophysiological manifestations of radiation toxicity. These processes are orchestrated by a plethora of interacting molecular signals, cytokines, chemokines, and growth factors, and involve many interacting cellular compartments, such as endothelial cells, the intrinsic and extrinsic nervous system, and various cells of the immune system.

(98) The salivary glands, liver, and pancreas also belong to the digestive system. The cellular organisation, radiation response, and radiation tolerance of these organs are fundamentally different from those of the alimentary tract organs. The main salivary glands include the parotid, submandibular, and sublingual glands. The glands are enclosed by a connective tissue capsule and are divided internally into lobules. The secretory components comprise serous and/or mucinous cells, surrounded by contractile myoepithelial cells. Their secretions enter the oral cavity through one or more excretory ducts.

(99) The human pancreas is located retroperitoneally in the upper abdomen. It contains an exocrine, acinar component that secretes digestive enzymes (e.g. trypsin, chymotrypsin, lipase, amylase) into the second part of the duodenum through the ampulla of Vater. The pancreas also contains an endocrine component, organised as circumscribed islets of Langerhans, which produces several important hormones, including insulin, glucagon, and somatostatin.

(100) The liver is the largest internal organ of the human body. It plays a critical role in body metabolism (e.g. glycogen storage, plasma protein synthesis, production of coagulation factors, detoxification, production of bile). Sheets of connective tissue divide the liver into thousands of lobules, the structural subunit of the liver. Lobules are roughly hexagonal in shape and contain portal triads (artery, portal vein, and bile duct) at the vertices and a central vein in the middle. Blood flows from the hepatic artery and portal veins through hepatic sinusoids, and empties into the central veins which coalesce into the hepatic veins. The liver is one of the few organs in the body that are capable of regeneration. Hence, hepatocytes are considered to be unipotent stem cells (or reverting postmitotic cells). While they do not regularly divide under normal conditions, they can be recruited into cell cycle and divide to produce two hepatocytes, thereby regenerating the organ from as little as 25% remaining tissue.

(101) The epithelial lining of the intestine covers an area approximately 200 times that of the surface of the skin, and is the most rapidly renewing system in the body, undergoing continuous, rapid turnover. Epithelial cells proliferate in the crypts, migrate along the villi, and are eventually shed into the intestinal lumen. Substantial experimental work, mainly in mice, has been undertaken to determine the proliferative characteristics of the intestinal epithelium. The cell-cycle time for the majority of proliferating cells in the mouse intestinal crypt is of the order of 12–13 h, whereas the cell-cycle time for crypt stem cells is considerably longer at approximately 24 h. The total transit time for cells from the crypt base to the villus tip is approximately 6–

8 days, and it takes 48–72 h from when a cell enters the villus base until it is shed from its tip (Potten, 1995). In human intestine, the crypts are larger than in the mouse, with a lower fraction of cells in the S phase of the mitotic cycle and a cell-cycle time of approximately 30 h (i.e. approximately 2.5 times that in mouse intestine) (Kellett et al., 1992).

(102) Acute radiation injury to the intestine manifests within days of exposure, when cells in the differentiated cellular compartment in the villus are no longer adequately replaced by cells from the progenitor compartment in the crypt. Radiation injury is rapidly recognised in the intestine by initiation of accelerated, compensatory proliferation (Hagemann et al., 1971; Hagemann, 1976), when the cycle times of crypt cells may be as short as 6 h (Leshner and Bauman, 1969). Stem cell doubling times are longer, up to approximately 24 h, because of the concomitant division of stem cells and their loss to the differentiation pathway (Potten et al., 1988).

(103) The relative importance of clonogenic death vs apoptosis in the intestinal epithelium and their relationship to the intestinal radiation response in the clinical situation are unclear. Studies in genetically modified mice suggest that intestinal crypt cell apoptosis does not play a major role in the intestinal radiation response (Rotolo et al., 2008; Kirsch et al., 2010). The issue is further complicated by the fact that many preclinical studies have been performed with single doses of radiation, a situation that differs substantially from fractionated radiation therapy as used in clinical cancer treatment. Temporal shifts in the relative significance of clonogenic cell death, apoptosis, start time and intensity of compensatory proliferation, and cell migration during courses of fractionated irradiation are factors that further complicate the extrapolation of animal experiments to the clinical situation.

2.2.2. Clinical data on therapeutic doses

Oral mucosa and oesophagus

(104) Historically, mucositis was viewed solely as an epithelium-mediated event that was the result of the effects of radiation on dividing epithelial progenitor cells. It was thought that loss of the renewal capacity of the epithelium resulted in cell loss and subsequent ulceration. However, while the early manifestations of radiation toxicity in the oral mucosa reflect the proliferation rate and transit cycle of the squamous epithelial lining, the complexities underlying mucosal barrier injury have only been appreciated recently. Increasing evidence supports the concepts that virtually all cells and tissues of the oral mucosa, including the extracellular matrix, contribute to barrier injury, and that nothing occurs within the mucosa as a biologically isolated event (Sonis et al., 2004). Despite the common use of the term ‘mucositis’ to denote early radiation injury, acute inflammatory infiltrates are not prominent during the early stages of radiation-induced mucositis, and mucositis occurs during periods of maximal myeloablation. The ulcerative stage of mucositis, on the other hand, is generally accompanied by robust infiltration of polymorphonuclear and round

inflammatory cells. Most patients who receive radiation therapy for head and neck cancer will develop acute mucositis.

(105) Delayed radiation-induced lesions in the oral mucosa commonly occur 6 months to 5 years after radiation therapy as a result of progressive vascular damage and tissue fibrosis. Delayed changes occur at total fractionated doses of >50 Gy (using 2 Gy/fraction), but chronic ulcers do not usually occur with fractionated total doses of <65 Gy (Cooper et al., 1995). Dental caries are also common after radiation therapy of tumours in the head and neck area. However, this complication is probably a consequence of salivary gland injury, resulting in a deficit in, and altered composition of, saliva (xerostomia), rather than a direct effect of radiation on the teeth.

(106) Fractionated irradiation suppresses cell production and reduces cell numbers in the oral mucosa during the first week of therapy, followed by partial restoration of proliferation and reduced rate of cell loss (Dorr et al., 2002). Interestingly, as for the intestine (Hovdenak et al., 2000), there is poor correlation between these cellular changes and patient symptoms.

(107) Several non-standard fractionation regimens (accelerated fractionation, hyperfractionation, and/or concomitant boosts) have been used in head and neck cancer for the purpose of optimising control rates of rapidly proliferating tumours. The rationale for these altered fractionation schemes is that tumour cell proliferation often occurs during conventionally fractionated radiotherapy, and constitutes a major obstacle to cancer cure (Knee et al., 1985; Peters et al., 1988). Non-standard fractionation regimens, particularly hyperfractionated regimens, appear to confer a survival benefit compared with conventional fractionation regimens (Bourhis et al., 2006). On the other hand, when such regimens involve dose escalation, they may be associated with excessive acute side-effects and some of the therapeutic gain is lost (Zimmermann et al., 1998).

(108) The squamous epithelium of the oesophagus has approximately the same turnover rate as the oral mucosa. Most patients who undergo mediastinal irradiation will develop odynophagia and dysphagia as signs of acute oesophagitis. After mediastinal irradiation alone, the threshold for acute radiation oesophagitis is approximately 40–45 Gy total dose in 2-Gy fractions. As the incidence of endoscopic changes is low, and motility and transit times do not generally change, it is assumed that the underlying basis for the acute oesophagitis may be related to nociceptive stimulation of the oesophageal mucosa (Yeoh et al., 1996a). Long-term sequelae after oesophageal irradiation are uncommon. However, delayed complications, mainly strictures, occur in patients who have received a radiation dose of >60 Gy (in 2-Gy fractions) (Fajardo et al., 2001). There is an inverse relationship between the radiation dose and time to stricture formation.

Gastrointestinal tract

(109) Acute radiation enteropathy occurs as a result of mitotic and apoptotic cell death in the crypt epithelium, resulting in insufficient replacement of the surface epithelium. Damage to the intestinal mucosa has been shown to occur at doses of >1 Gy. As with oral mucositis, it is not appropriate to view intestinal radiation

mucositis solely as an epithelial phenomenon. Breakdown of the mucosal barrier facilitates penetration of antigens, bacterial products, and digestive enzymes from the intestinal lumen into the intestinal wall and initiates the manifestations of intestinal radiation mucositis. Moreover, changes in motility, which often precede the development of histopathological changes, appear to play an important role in the symptomatology of acute radiation enteropathy (Erickson et al., 1994). Symptoms of acute bowel toxicity occur in most patients during treatment of intra-abdominal or pelvic neoplasms. While these symptoms may be severe enough to require significant supportive care, and sometimes de-intensification of the treatment, they are usually transient and cease shortly after completion of radiation therapy. If a large volume of intestine is exposed to radiation, such as may occur in non-therapeutic (accidental or other) irradiation scenarios, a rapidly fatal syndrome develops, consisting of secretory diarrhoea, bacterial translocation, and intestinal haemorrhage.

(110) Major compensatory physiological and proliferative responses occur during a course of radiotherapy, and significant restitution of the intestinal mucosa actually occurs during ongoing fractionated radiation therapy. Hence, despite increasing symptoms of bowel toxicity and continued daily irradiation, intestinal permeability and histological injury are maximal in the middle of the radiation course, but may regress significantly towards the end (Carratu et al., 1998; Hovdenak et al., 2000). These observations not only demonstrate the powerful compensatory responses of epithelial proliferation and mucosal adaptation, but also show that mechanisms other than obvious changes in mucosal structure and function must contribute to symptoms in patients who undergo pelvic or abdominal radiation therapy.

(111) Delayed radiation injury of the gastrointestinal tract occurs at least 3 months after radiation therapy, but usually several months or years after exposure. Common manifestations of delayed gastrointestinal toxicity include malabsorption, maldigestion, dysmotility, intestinal obstruction, intestinal perforation, and fistula formation. The basis of these manifestations includes mucosal atrophy, chronic mucosal ulcerations, intestinal wall fibrosis, and stricture formation. The pathogenesis of chronic radiation enteropathy is considerably more complex than that of the acute radiation response. Again, vascular and connective tissue damage are central, but structural alterations occur in most compartments of the intestinal wall (Denham and Hauer-Jensen, 2002). Intestinal dysmotility during the chronic phase of injury may cause proximal bacterial overgrowth, and contribute to diarrhoea and malabsorption (Husebye et al., 1994, 1995). Delayed radiation enteropathy may progress to complications that require surgical intervention or long-term parenteral nutrition, in which case the long-term prognosis is poor (Galland and Spencer, 1985; Harling and Balslev, 1988; Jahnson et al., 1992; Silvain et al., 1992; Regimbeau et al., 2001; Larsen et al., 2007).

(112) While the traditional notion was that acute and delayed tissue injury are unrelated, the concept of consequential injury in the intestine was suggested based on experimental evidence (Osborne et al., 1970) and clinical observation (Kline et al., 1972). Subsequent clinical studies (Bourne et al., 1983; Wang et al., 1998; Weiss et al., 1999) and preclinical studies (Hauer-Jensen et al., 1983, 1985; Travis

and Followill, 1991; Wang et al., 1999; Denham et al., 2000) showed that acute injury often contributes to development of delayed changes. A pathophysiological approach to normal tissue injury that accommodates all types of injury (early, delayed, and consequential) has been proposed (Denham et al., 2001).

(113) The incidence and severity of delayed intestinal radiation toxicity depends on radiation dose, volume of bowel irradiated, fractionation schedule, concomitant chemotherapy, as well as comorbidities and other patient factors. Most patients who receive radiation therapy of tumours in the abdomen, pelvis, or retroperitoneum experience some manifestations of acute bowel toxicity. Patients with inflammatory bowel disease have an inordinately high risk of severe intestinal toxicity (Willett et al., 2000), and tobacco smoking is a strong predictor of major radiation-induced complications (Eifel et al., 2002). As one may expect based on the pathophysiology of the respective lesions, there appears to be a volume effect for some forms of chronic diarrhoea, but not for strictures (Letschert et al., 1994). Recent advances in treatment planning and delivery techniques have helped to reduce the incidence of serious radiation-induced intestinal complications. However, it is important to recognise that only a fraction of patients suffering from less severe postradiation intestinal dysfunction seek medical attention. After radiotherapy of abdominal tumours, chronic symptoms or signs of intestinal dysfunction are present in 60–90% of patients (Yeoh et al., 1993; Fransson and Widmark, 1999), suggesting that chronic intestinal injury is an almost inevitable consequence of abdominal radiation therapy. Many patients alter their dietary habits and accept restriction to their normal daily activities without expectation of successful intervention.

(114) Radiation proctitis, although pathogenically similar to injury elsewhere in the bowel, has distinct features. The acute symptoms/signs consist mainly of loose stools, sometimes with haematochezia, tenesmus, and rectal pain. The chronic symptoms/signs are anorectal dysfunction (urgency, incontinence, sphincter dysfunction), rectal haemorrhage, and formation of strictures or fistulas. Most patients who receive pelvic radiation therapy have signs of acute radiation proctitis (Yeoh et al., 1998; Hovdenak et al., 2000). Similar to intestinal radiation injury, systematic studies of anorectal function in patients who have undergone pelvic radiation therapy also show a high incidence of chronic dysfunction (Yeoh et al., 1996b, 2000, 2004).

(115) Androgen therapy of prostate cancer appears to influence both acute and chronic radiation proctitis (Sanguineti et al., 2002; Peeters et al., 2005). The rectum generally exhibits a rather pronounced volume effect, and there are also important issues related to ‘volume effects’ with partial circumference irradiation, such as encountered during prostate seed implant therapy (Waterman and Dicker, 2003) or conformal radiotherapy of prostate cancer (Wachter et al., 2000). Studies of dose–volume histograms indicate that rectal toxicity depends strongly on the volumes of rectal wall receiving doses of >70 Gy (in ≤ 2 -Gy fractions), as well as on the ‘reserve’ of unexposed rectal tissue (Jackson, 2001). The incidence of rectal toxicity also appears to be influenced by the volumes exposed to intermediate doses (40–50 Gy), because these regions may interfere with the repair of the effects in a central high-dose region (Jackson et al., 2001).

Salivary glands, pancreas, and liver

(116) The acinar cells of the parotid gland are mainly serous. The submandibular gland contains both serous and mucinous acinar cells, while the sublingual gland is predominantly mucinous. Both types of acinar cells have very low turnover rates, but serous acinar cells are much more radiosensitive than mucinous cells. Acute manifestations of salivary gland irradiation include inflammation (swelling, tenderness, and pain) accompanied by dryness in the mouth, reduced salivary flow, and elevated serum amylase levels. Salivary output often begins to decrease after a few days of radiation therapy and reaches a nadir after 6–8 weeks (Franzen et al., 1992; Cooper et al., 1995). The radiation doses that are associated with permanent loss of salivary gland function at 5 years in 5% and 50% of patients are 45 Gy and 60 Gy, respectively (Cooper et al., 1995; Fajardo et al., 2001).

(117) Until recently, relatively little was known about the early response of the human pancreas to ionising radiation. However, the development of non-invasive and minimally invasive tests has allowed evaluation of the early effects of radiation on pancreatic function (Horst et al., 2002). After pancreatic irradiation, chronic pancreatitis and pancreatic exocrine insufficiency occurs after 40–50 Gy, and acinar atrophy and pancreatic fibrosis generally occurs after doses in the range of 50–60 Gy (Fajardo and Berthrong, 1981; Levy et al., 1993). The larger excretory ducts of the pancreas and the islets of Langerhans are relatively radioresistant.

(118) Turnover of hepatocytes is normally slow, so acute radiation injury of the liver does not reflect clonogenic cell death. Rather, radiation-induced liver disease typically presents subacutely, approximately 3 months after the beginning of radiation therapy, as a condition called ‘veno-occlusive disease’. Pathologically, the hallmark features of veno-occlusive disease are areas of centrilobular congestion and necrosis. In severe cases, these lesions may progress to frank liver failure. The liver exhibits a prominent volume effect and the threshold for injury is low when most or all of the organ is exposed to radiation. For whole-liver exposure with conventionally fractionated radiotherapy, total doses of 28–30 Gy are associated with a 5% incidence of liver disease (Marks et al., 2010b; Pan et al., 2010). If only one-third of the liver is exposed, the dose for a 5% incidence of damage increases to >42 Gy, and if <25% of the effective liver volume is irradiated, much higher doses of radiation are well tolerated (Dawson and Ten Haken, 2005). However, pre-existing liver dysfunction has been shown to increase susceptibility to radiation-induced liver damage. The regenerating liver, such as after resection, is also significantly less tolerant (Tefft et al., 1970), and experimental studies have shown that latent radiation injury of the liver can be unmasked by a subsequent resection when the remaining liver cells are stimulated to divide (Weinbren et al., 1960).

(119) Emami et al. (1991) summarised some of the data regarding tolerance of the digestive tract organs. While the specific figures have been subject to considerable debate, the original table nevertheless provided a reasonable indication of relative radiosensitivities and tolerance doses. These tolerance doses only applied to situations where radiation therapy was used alone, and not to patients who received concomitant chemotherapy or biological therapy. More recently, a comprehensive effort

to develop systems of more accurate, evidence-based tolerance dose estimates for various organs was undertaken by the QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) group. The QUANTEC reviews constitute a series of articles about general principles, and articles with organ-specific clinical data, including several pertaining to the digestive system (Deasy et al., 2010; Kavanagh et al., 2010; Michalski et al., 2010; Pan et al., 2010; Rancati et al., 2010; Werner-Wasik et al., 2010). The tables contained in the various organ-specific QUANTEC reviews, together with the published summary table of dose/volume/outcome data (Marks et al., 2010b), provide a more contemporary way to estimate dose–volume relationships for the digestive tract.

2.2.3. Experimental data and mechanisms of damage

(120) A substantial body of experimental work has been performed to investigate cellular pathogenesis (Potten and Hendry, 1995) and time–dose–fractionation relationships in the irradiated oral mucosa and intestine. There is a direct relationship between radiation dose and survival of intestinal crypts (Withers and Elkind, 1968, 1969, 1970). Fractionation sensitivities are low, giving high α/β ratios in the range of 6–11 Gy for early reactions (Thames and Withers, 1980; Fowler, 1989). In contrast, these rapidly proliferating tissues are sensitive to changes in overall treatment time during fractionated irradiation, and the ‘extra’ doses required to counteract repopulation after a lag period are generally high. These experimental studies are entirely consistent with clinical data demonstrating a substantial influence of overall treatment time on the development of oral mucositis after irradiation of head and neck cancer (Bentzen et al., 2001).

(121) Studies on the response of the mouse tongue epithelium have confirmed the concept of consequential late effects in the oral mucosa, demonstrated a remarkable capacity for cellular repopulation, and pointed to dose intensity as an important factor in the repopulation response (Dorr and Kummermehr, 1990; Dorr and Weber-Frisch, 1995a,b).

(122) The response of the rat stomach to localised single and fractionated doses has been assessed (Breiter et al., 1993). In the second and third week after irradiation, acute gastritis developed which resulted in a dose-dependent loss of body weight. The α/β value for dose fractionation, using a 10% reduction in body weight as the endpoint, was approximately 10 Gy. Between 4 and 40 weeks after irradiation, subchronic radiation damage was observed which presented itself as atonic dilatation of the stomach. For this effect, the α/β value was 4.8–5.3 Gy. In a five-fraction experiment, a significant increase in tolerance amounting to 0.8 Gy/day for the acute effect and 0.4 Gy/day for the subchronic effect was observed when interfraction intervals were increased from 1 day to 1 week.

(123) Experiments investigating the late tolerance of rat rectum to external or intracavity irradiation were analysed to calculate dose–time–fractionation characteristics (Dubray and Thames, 1994). The endpoint was late rectal stenosis in female Wistar rats. The fractionation sensitivity was higher than for early reactions (α/β values ranged from 2.7 to 6.7 Gy), and there was a significant sparing effect of

treatment protraction. It was considered that the sparing effect could have been due to repopulation when treatments were longer than 5 days (dose recovered per day due to proliferation was 0.61–1.08 Gy/day in fractions of 4 Gy), or another possibility was that the radiosensitivity might have changed during treatment. It was concluded that the radiobiological features of late stenosis in the rats were consistent with combined injuries of early- and late-responding components of the rectal wall.

(124) In the intestine, consequential injury also contributes substantially to delayed intestinal fibrosis, which is therefore associated with a high α/β ratio (Hauer-Jensen et al., 1988, 1990; Langberg et al., 1992). Fraction size mainly affects delayed injury, whereas overall treatment time affects both early and delayed radiation responses (Langberg et al., 1994; Langberg and Hauer-Jensen, 1996a). Hyperfractionated regimens with interfraction intervals of 6 h or more confer optimal sparing of intestinal injury (Langberg and Hauer-Jensen, 1996b). When small bowel has to be included in the treatment field, concomitant boost (additional dose applied to the tumour for part of the fractionated treatment schedule) should be applied towards the end of the radiation schedule, after the onset of compensatory proliferation, rather than at the beginning (Allgood et al., 1996).

(125) Many mechanistic studies have been performed to reveal potentially important information about the radiation response of gastrointestinal tract organs. This includes volume effects, studied in detail in the colorectum (Skwarchuk and Travis, 1998). Several studies also have application to organs outside the digestive tract. For example, the first direct proof of involvement of the fibrogenic cytokine, transforming growth factor β (TGF- β), in radiation fibrosis was obtained in a model of radiation-induced bowel injury (Zheng et al., 2000).

(126) A particularly interesting debate revolves around the role of microvascular injury in the intestinal radiation response. The debate originated from a report that mice deficient in the enzyme acid sphingomyelinase were protected against radiation-induced endothelial cell apoptosis and exhibited decreased lethality after TBI (Paris et al., 2001). As endothelial cell apoptosis, but not apoptosis of the crypt epithelium, is dependent on the sphingomyelin, the initial interpretation of this finding, together with a substantial body of additional supportive evidence, was that endothelial cell apoptosis is a major contributor to early intestinal radiation toxicity. The increased survival of irradiated crypt epithelial clonogens after injection of basic fibroblast growth factor (bFGF) was assumed to be due to endothelial rescue (Maj et al., 2003). Further, it was argued that in *ATM*^{-/-} mice, the crypt epithelial clonogenic cells had increased apoptotic radiosensitivity due to the inability to suppress ceramide production in the absence of ATM protein (Ch'ang et al., 2005), and the critical radiation target then switched from the endothelial cells to the crypt epithelial clonogenic cells in these mice.

(127) However, the role of endothelial cell apoptosis remains controversial. For example, there have been recent studies to selectively irradiate the vasculature using intravascular boronated liposomes and epithermal neutrons, yielding short-range charged particles (Schuller et al., 2007). The calculated dose to the endothe-

lial cells in these studies was increased by ~ 3.3 -fold compared with the total-body dose. The authors reported no marked endothelial cell apoptosis at 4–8 h after 1–33 Gy. The low average level of 1.6 apoptotic cells per villus above a non-irradiated background level of 0.12 was found to be due to apoptosis in CD45-positive leukocytes. These authors had previously demonstrated that high doses to the endothelial cells neither increased epithelial clonogenic cell killing nor caused excess lethality in whole-body irradiated mice (Schuller et al., 2006). One other laboratory also failed to find high levels of radiation-induced endothelial cell apoptosis in the intestine (Potten, 2004). It is possible that technical reasons are responsible for some of the discordant results. Detection of apoptotic endothelial cells in situ may be difficult for a variety of reasons, and alternative in-vivo detection methods have been proposed (Diamant et al., 2004; Horstmann et al., 2004). However, Kirsch et al. (2010) reported that selective deletion of pro-apoptotic proteins (Bak1 and Bax) from either endothelial cells or gastrointestinal epithelium did not protect mice from developing the gastrointestinal radiation syndrome. In contrast, selective deletion of p53 from the gastrointestinal epithelium, but not from endothelial cells, sensitised mice to the acute gastrointestinal radiation syndrome. These authors concluded that the gastrointestinal radiation syndrome is caused by death of gastrointestinal epithelial cells, and that the cells die by a mechanism that is independent of apoptosis but regulated by p53.

(128) It is well known from other areas of gastrointestinal pathophysiology that genetic manipulations or pharmacological interventions that preserve the intestinal microcirculation after an insult have a protective effect on the gut epithelium and the intestinal mucosa. On the other hand, while endothelial cell apoptosis is observed in many inflammatory and immune disorders, only limited experimental evidence is available to suggest that it is critical to the pathogenesis of such diseases (Winn and Harlan, 2005). It is possible that radiation-induced endothelial cell apoptosis might indicate a state of dysfunction of the intestinal microvasculature, which in turn may influence the radiation tolerance and/or repair capacity of the crypt epithelium. Clarifying the reasons for the differences in the results obtained by Schuller et al. (2006, 2007), which are essentially consistent with the long-established role of epithelial cells in the gastrointestinal radiation syndrome, and those reported by Paris et al. (2001), which present a new paradigm, is important because the mechanism of intestinal radiation injury has implications for its prophylaxis and mitigation in cases of therapeutic or unplanned radiation exposures.

2.2.4. Gastrointestinal injury after whole-body radiation exposure

(129) In most TBI exposure scenarios, injury to the gastrointestinal tract is one of two primary determinants of survival (together with the haematopoietic/immune system). The gastrointestinal tract plays a prominent role in the response to TBI in several ways. First, it is responsible for the prodromal effects seen after low (1 Gy) radiation doses. Second, the gastrointestinal syndrome develops after exposure to radiation doses of >6 Gy (in humans). It is associated with extensive destruction

of the mucosa, severe secretory diarrhoea, and loss of fluids and electrolytes. Third, and perhaps most importantly, gastrointestinal injury plays a significant role in the pathophysiology of the response to radiation doses in the 'haematopoietic' dose range (2–10 Gy in humans). While radiation doses of up to 6 Gy do not result in development of the full gastrointestinal radiation syndrome, breakdown of the mucosal barrier converts the intestine into a large pro-inflammatory organ that releases cytokines and other inflammatory mediators into the circulation. Moreover, translocation of bacteria from the bowel lumen to the systemic circulation is common, and sepsis from enteric micro-organisms (usually enterobacteriaceae) is an important cause of death after radiation doses in the 'haematopoietic' dose range.

(130) The prodromal symptoms seen after TBI consist of nausea, emesis (vomiting), and diarrhoea. The time of onset, duration, and severity of the prodromal symptoms are directly related to the radiation dose, and this has been proposed as a fairly reliable indicator of the radiation dose received for use in the clinic. Nevertheless, the time to onset of prodromal symptoms should be used with caution for predicting the radiation dose received by individual patients (Demidenko et al., 2009). The exact mechanism of radiation-induced emesis has not been fully elucidated, but studies in various animal models suggest triggering of the 'vomiting centre' in the area postrema near the fourth ventricle in the brain by a combination of humoral and neural stimuli. The prodromal diarrhoea is related to changes in gastric emptying and intestinal motility, the pathogenesis of which also appears to involve neurohumoral mechanisms.

(131) Survival is extremely unlikely with the full-fledged TBI-induced gastrointestinal radiation syndrome. Death usually occurs before day 10, mostly around 5–7 days after irradiation. Destructive changes of the intestinal epithelial lining cause breakdown of the mucosal barrier that normally separates the contents of the intestinal lumen from the gastrointestinal tissue, resulting in severe secretory diarrhoea, dehydration, and electrolyte imbalance. In addition to denudation of the mucosa, the loss of fluids and electrolytes occurs as a combination of changes in cellular transport processes, neurogenic mechanisms, release of peptide hormones and other mediators, action of bile and pancreatic secretions, and alterations in splanchnic blood flow. Although bacteraemia does occur, it is infrequent and, while fluid and electrolyte therapy may postpone death, antibiotics do not reduce lethality of the classical gastrointestinal radiation syndrome.

(132) Although intestinal irradiation is necessary and sufficient to produce what is commonly referred to as the 'gastrointestinal radiation syndrome' (Quastler et al., 1951), and surgical removal of the exposed bowel can prevent the syndrome from occurring (Osborne, 1956), it is firmly established that lethality from bowel toxicity is heavily influenced by radiation injury to other organ systems (e.g. the haematopoietic system) (Terry and Travis, 1989). It is important to recognise that reference to the 'gastrointestinal radiation syndrome' and the 'haematopoietic radiation syndrome' simply indicates that toxicity in those organ systems predominate clinically, but that the pathophysiological manifestations depend heavily on interactions between multiple cell types and organ systems in the body. This is the basis for the central role of the gastrointestinal tract in radiation doses in the 'haematopoietic' dose

range. The role of gastrointestinal radiation toxicity from the perspective of the radiation-induced multiple organ dysfunction syndrome has been described (Monti et al., 2005).

(133) Information on non-cancer disease incidence and mortality is also available from cohorts of atomic bomb survivors (Shimizu et al., 1999; Preston et al., 2003; Yamada et al., 2004). While questions have been raised with regard to the shape of the dose–response curve (Stewart, 1997), the only major difference in terms of gastrointestinal disease is a higher prevalence of hepatitis B and hepatitis C infection, and liver cirrhosis among atomic bomb survivors. Interestingly, there is indirect evidence to support the notion of radiation-induced reactivation of hepatitis virus (Kim et al., 2007), and that the mechanism of reactivation may involve the release of IL-6 from irradiated endothelial cells (Chou et al., 2007). These data could conceivably provide an explanation for the higher than expected prevalence of hepatitis and chronic liver disease among atomic bomb survivors.

2.2.5. Internal exposure

(134) Internal exposure of the gastrointestinal tract to radiation from inside the lumen occurs when radionuclides are ingested, inhaled, and subsequently exhaled from the lungs to the alimentary tract, or in situations where radionuclides are excreted into the bowel. Conversely, when radionuclides are applied intraperitoneally for cancer treatment, the serosal surface of the alimentary tract organs may be exposed. There is an extensive treatise on the internal exposure to radiation in ICRP *Publication 100* (ICRP, 2006).

(135) The extent of absorption, site of absorption, secretion, and retention of radionuclides depend on the chemical properties of the element and on the specific chemical form of the intake. For most elements, the small intestine is the predominant site of absorption. Based on experiments with rats and dogs (LD_{50/10} endpoint), the LD₅₀ for ingestion of beta emitters, such as ¹⁰⁶Ru/¹⁰⁶Rh (average 1.4 MeV beta) or ¹⁴⁷Pm (average 0.06 MeV beta), was approximately 35 Gy, estimated as dose to crypt cells. The dose to the villus epithelium may be three- to four-fold higher. The dose to the crypt epithelium is comparable with the LD_{50/7} after external irradiation (11–15 Gy) when the reduction in effect at the lower dose rate is taken into account.

(136) There are few reports of acute injury to the intestinal mucosa after radionuclide ingestion in humans. Of 22 individuals with extensive internal contamination with ¹³⁷CsCl (>3.1 MBq) in the Goiania accident in Brazil, eight developed nausea, vomiting, and watery diarrhoea during the prodromal phase. Doses received by these individuals, estimated by cytogenetic dosimetry, were in the range of 3–7 Gy, accumulated over a period of 2 weeks. In four people who received estimated doses of 4–6 Gy and who died of radiation injuries, intestinal bleeding was found at autopsy (Brandao-Mello et al., 1991). Administration of beta-emitting radionuclides into the peritoneal cavity for cancer therapy is associated with mild-to-moderate radiation sickness and neutropenia when doses in the range of 50–70 Gy are used

(UNSCEAR, 1982). The amount of radiation to which the intestinal mucosa is exposed in each situation would vary with the energy of the beta emitter, as well as with the presence of loculations from peritoneal adhesions and other local factors.

(137) Information about internal exposure of the liver in humans is available from patients who have received intra-arterial injection of radionuclides such as ^{32}P or ^{90}Y for hepatic malignancies, injection of ^{224}Ra for ankylosing spondylitis or tuberculosis, or thorotrast angiography. While some of these patients developed non-malignant liver disorders, it is difficult to draw conclusions relative to dose–response relationships and specificity of the response.

2.2.6. Summary

(138) The number of tumours treated with radiation therapy with parts of the gastrointestinal tract included in the treatment field is high. Consequently, early radiation toxicity in these organs is a major dose-limiting factor of considerable clinical importance. Moreover, because the survival prognosis of patients with tumours in the abdomen or head and neck area is generally rather favourable, delayed toxicity, mainly in the form of postradiation fibrosis, constitutes an obstacle to uncomplicated cancer cure in an exponentially growing cohort of long-term cancer survivors. Finally, because of the radiosensitivity of the epithelial barrier and the importance of sepsis from intestinal bacteria as a cause of death after radiation exposure, the intestine has become recognised as a critical organ in the response to TBI and in combined injury situations. This has caused a resurgence of interest in the gastrointestinal radiation response as it pertains to radiological nuclear terrorism or accident scenarios.

2.3. Reproductive system

2.3.1. Anatomical features and proliferative organisation

(139) The male genital system consists of three groups of organs: gonads (testicles); sperm storage and ejaculation organs (epididymis, deferent duct, and ejaculatory duct); and seminal vesicles, prostate gland, and penis. The testes are composed of two structurally distinct but functionally related compartments: the seminiferous tubule and the intertubular space. The intertubular space accommodates the vasculature, lymphatics, and testosterone-producing Leydig cells. The seminiferous tubules, of which there are approximately 500 in each testis, are convoluted loops that converge and drain spermatozoa into the rete testis. The tubules are lined by seminiferous epithelium, consisting of various types of male germ cells (spermatogenic cells) and a single type of supporting cell, the Sertoli cell. Spermatogenesis is a complex process by which diploid germ cell spermatogonia undergo proliferation and differentiation into mature haploid spermatozoa. This highly co-ordinated process, taking approximately 74 days in humans, can be divided into three phases: mitotic proliferation of spermatogonial stem cells to yield primary spermatocytes;

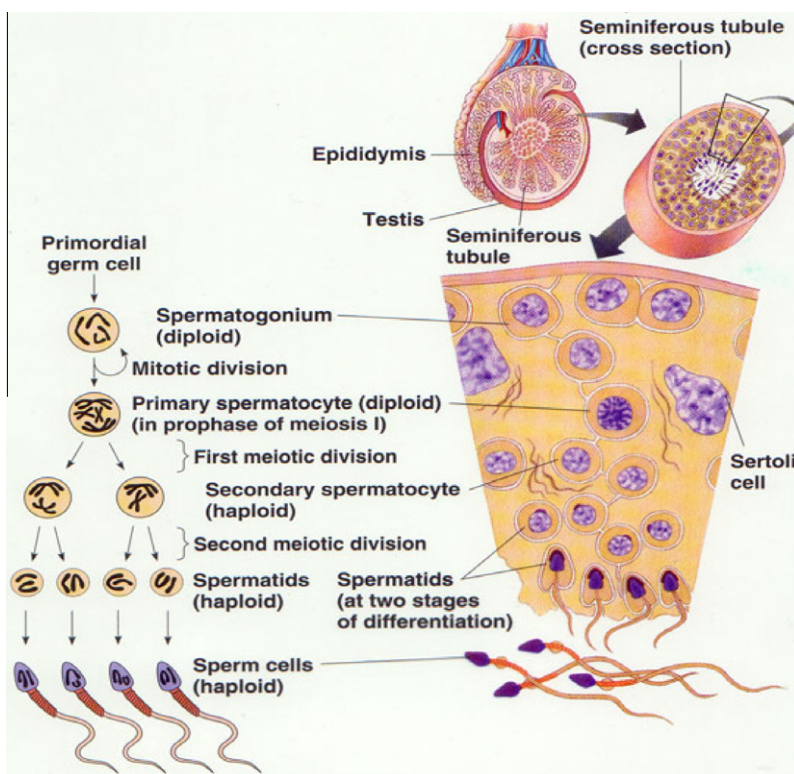


Fig. 2.2. Diagrammatic representation of human spermatogenesis. Source: <http://iceteazegeg.files.wordpress.com/2009/02/spermatogenesis.jpg>.

meiotic maturation of spermatocytes to yield round spermatids; and differentiation of spermatids into mature spermatozoa, known as spermiogenesis (Fig. 2.2).

(140) The functions of the female genital system include childbearing and breast-feeding, as well as gametal cell production and hormone synthesis. The female genital system consists of ovaries, fallopian tubes, uterus, vagina, external sex organs, and breasts. The formation of an ovule, as well as production of sex hormones, takes place in the ovaries. The ovarian cycle in sexually mature individuals includes growth of follicles, ovulation, and formation of the corpus luteum (Fig. 2.3). Fallopian tubes capture the ovum during ovulation and ensure its passage into the uterine cavity. The development of the embryo and fetus takes place in the uterus. The walls of the fallopian tubes and the uterus are composed of three membranes: the mucous membrane lined with a single layer of columnar epithelium; the muscular membrane; and the serous membranes. The mucous membrane of the vagina is lined with multilayer non-keratinising epithelium. The structure of the mammary glands changes with age and phase of the menstrual cycle.

(141) Radiotherapy may damage gonadal tissue at all ages and result in long-lasting or permanent sterility in both males and females (Rowley et al., 1974; Wallace

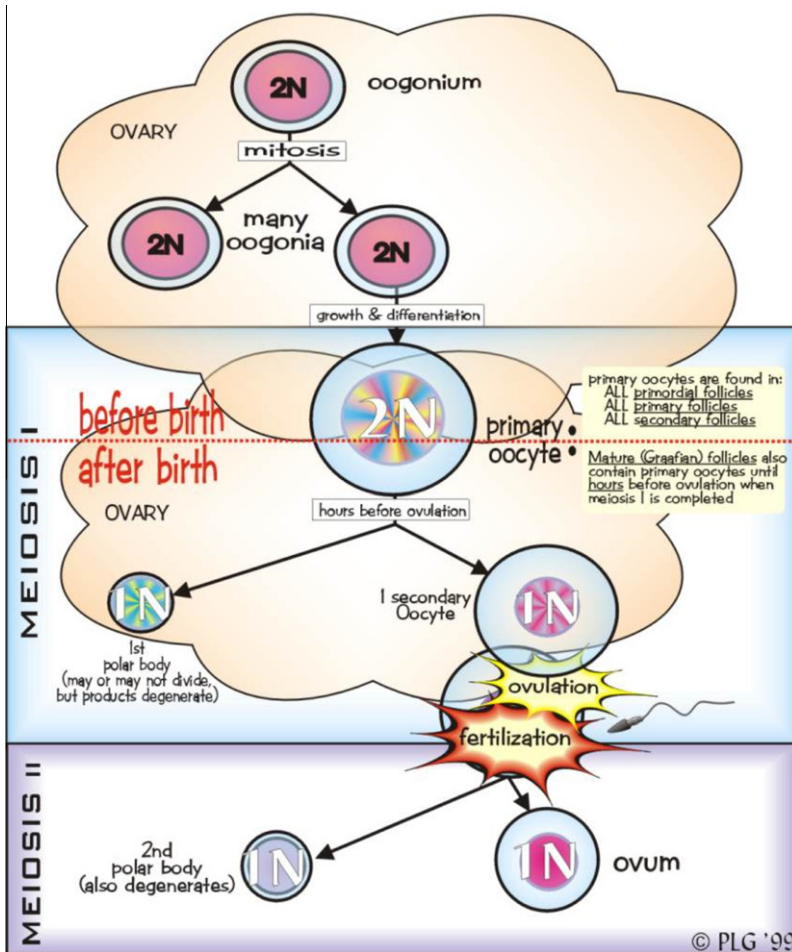


Fig. 2.3. Diagrammatic representation of human oogenesis. Permission for reproduction given by Pamela Gregory, Tyler Junior College. Source: <http://science.tjc.edu/images/reproduction/oogenesis.jpg>.

et al., 1989a,b). The effects of chronic irradiation on the reproductive and sexual functions of human gonads have been studied in radiologists, nuclear workers, people exposed during radiation accidents, and patients treated with radiotherapy. One of the most frequently encountered and psychologically traumatic late complications following radiotherapy treatment for cancer is infertility.

2.3.2. Radiation-induced testicular damage

(142) The testicular germinal epithelium lining is very sensitive to irradiation, and the extent and duration of radiotherapy-induced testicular damage depends on the treatment field, total dose, and fractionation schedule (Speiser et al., 1973; Rowley

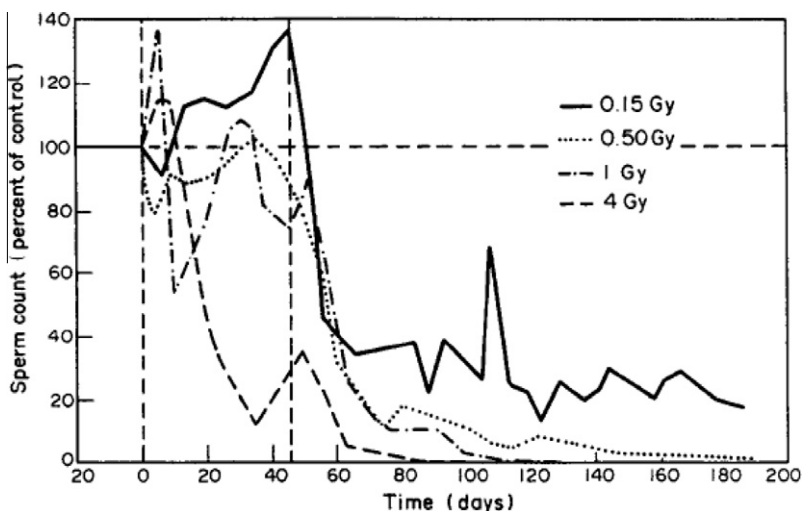


Fig. 2.4. Time course of sperm counts in normal men following high-intensity exposure of the testes to various doses of 190 kVp x rays (Heller, 1967; ICRP, 1984).

et al., 1974; Clifton and Bremner, 1983; Centola et al., 1994). The only known example of detailed radiosensitivity/time-course measurements for human spermatogenesis is shown in Fig. 2.4.

(143) Spermatogenesis is unusual in showing an inverse fractionation effect, whereby small fractions of dose are more damaging than the total dose given as a single dose (Lushbaugh and Ricks, 1972). This is considered to be due to stem cells progressing into radiosensitive stages. Therapeutic irradiation of the abdomen and inguinal area after unilateral orchidectomy causes transient oligozoospermia, and even azoospermia, at doses to the remaining testicle of 0.1–0.35 Gy. Recovery of spermatogenesis occurs 2–3 years later, with the recovery time increasing with the total dose (Herrmann, 1997). Doses as low as 0.1–1.2 Gy damage dividing spermatogonia and disrupt cell morphology resulting in oligozoospermia (Centola et al., 1994). Complete recovery of spermatogenesis was observed 9–18 months after a single dose of 1 Gy, by 30 months after doses of 2–3 Gy, and at 5 years or more after a 4-Gy dose (Speiser et al., 1973; Centola et al., 1994).

(144) Leydig cells are more resistant to damage from radiotherapy than the germinal epithelium. Susceptibility to radiation-induced damage of the Leydig cells appears to be inversely related to age, or sexual maturation, with greater damage following smaller doses in prepubertal boys. There may be progression through puberty with normal development of secondary sexual characteristics and preservation of potency despite severe impairment of spermatogenesis and infertility. Testicular irradiation with fractionated doses of >20 Gy is associated with Leydig cell dysfunction in prepubertal boys, while Leydig cell function is usually preserved up to fractionated doses of 30 Gy in sexually mature males (Shalet et al., 1989; Castillo et al., 1990). Prepubertal males who received TBI in preparation for BMT for

haematological malignancies developed normal secondary sexual characteristics. However, despite clinical evidence of intact Leydig cell function and normal testosterone levels, levels of luteinizing hormone (LH) were elevated in the majority of subjects, indicating mild Leydig cell dysfunction (Sarafoglou et al., 1997). Clinical assessment of patients rendered azoospermic following cytotoxic cancer therapy demonstrated markedly reduced testicular volumes (<12 ml). The absence of spermatogonial stem cells in testicular biopsies after irradiation suggests complete ablation of the germinal epithelium and irreversible infertility. Endocrine manipulation to enhance recovery of spermatogenesis may be successful in patients in whom the testicular insult is less severe if there is preservation of spermatogonial stem cells.

(145) The mechanisms of radiotherapy-induced damage to the testis have been explored in a number of animal studies (Bianchi, 1983; Meistrich, 1993). Irradiated testes show considerable capacity for recovery. The time course and extent of recovery will depend upon the exposure dose and the surviving stem spermatogonial pool in an appropriate supportive environment. In rats, it has been shown that some germ cells can survive cytotoxic therapy, including irradiation, and that the resulting azoospermia is a consequence of the inability of those spermatogonia that are present to proliferate and differentiate. Suppression of the hypothalamic–pituitary–gonadal axis, with gonadotrophic-releasing hormone (GnRH) agonists or antagonists, potentially facilitates recovery of spermatogenesis by reducing intratesticular testosterone concentrations (Meistrich, 1998). However, application of this approach in humans has been unsuccessful (Thomson et al., 2002).

(146) A number of animal studies have reported that the radiosensitivity of male gametes depends on their proliferation rate and differentiation status at the time of exposure, with the proliferating spermatogonia being the most radiosensitive (Nefedov et al., 2000). However, gonadal tissue is susceptible to radiotherapy at all ages. Detailed studies of marmoset monkeys, which exhibit a similar testicular developmental profile to the human male, have demonstrated significant development/maturation of Sertoli/stem spermatogonia and Leydig cells during the relatively ‘quiescent’ prepubertal stage. This provides an explanation for the vulnerability of the prepubertal testis (Kelnar et al., 2002).

2.3.3. Radiation-induced damage to the female reproductive tract

(147) Intact ovarian function demands a critical mass of primordial follicles in an appropriate endocrine milieu. The human ovary has a fixed oocyte pool at birth, which begins an atretic process culminating in menopause at around 50 years of age. Radiation may damage the ovary and hasten oocyte depletion resulting in loss of hormone production and premature menopause (Thomson et al., 2002). The ovaries may be damaged following TBI or abdominal or pelvic irradiation, and the extent of the damage is related to the radiation dose, fractionation schedule, and age at treatment. The human oocyte is very sensitive to radiation, with an estimated LD₅₀ of <2 Gy (Wallace et al., 1989a,b, 2003). The number of primordial

follicles present at the time of treatment (proportional to age), together with the dose received by the ovaries, will determine the fertile 'window' and influence the age of premature ovarian failure. Ovarian failure has been reported in 90% of patients followed-up for long times after TBI (10–15.75 Gy, ~2 Gy/fraction) and in 97% of females treated with fractionated total-abdominal irradiation (20–30 Gy, 1–2 Gy/fraction) during childhood (Wallace et al., 1989a). The younger the child at the time of radiotherapy, the larger the oocyte pool and the later the onset of premature menopause. It is now possible to predict the size of the primordial follicle reserve after a given dose of radiotherapy at any given age, based on the mathematical solution to the Faddy–Gosden model for natural oocyte decline (Faddy et al., 1992). This will help clinicians to provide accurate information when counselling women about fertility following radiotherapy treatment (Wallace et al., 2005).

(148) A number of women may have preservation of ovarian function if the dose to one or both ovaries can be relatively spared (e.g. in spinal or flank irradiation). However, even if the woman is able to conceive, the pregnancy is still beset with risks. The uterus is at significant risk of damage following TBI or abdominal or pelvic irradiation in a dose- and age-dependent manner (Critchley and Wallace, 2005). Uterine function may be impaired following fractionated radiation doses of 14–30 Gy as a consequence of disruption to the uterine vasculature and musculature elasticity (Critchley et al., 1992; Bath et al., 1999). Even lower doses of irradiation have been reported to cause impaired growth and blood flow (Critchley and Wallace, 2005). It is now established that uterine radiation in childhood increases the incidence of nulliparity, spontaneous miscarriage, and intrauterine growth retardation (Hawkins and Smith, 1989; Chiarelli et al., 2000; Green et al., 2002). Efforts to improve uterine function have been made with limited success. In young adult women, physiological sex steroid replacement therapy improves uterine function (blood flow and endometrial thickness) which may potentially enable these women to benefit from assisted reproductive technologies. Patients should be counselled accordingly and managed as high-risk pregnancies by an obstetrician aware of the potential problems.

(149) Studies in experimental animals have shown a wide range of oocyte radiosensitivities between species (Bianchi, 1983). Oocytes die by apoptosis after irradiation (Hanoux et al., 2007), and they are removed by phagocytosis within a few days. Earlier stages of development of oocytes are more radiosensitive than later stages. The population of oocytes declines with increasing age, and this causes lower radiation doses to be required to cause infertility in older females. A reduced level of damage is observed in mice after fractionated or protracted exposures compared with acute single doses, but the reverse is found in monkeys, and there is no evidence of recovery with dose protraction in humans.

2.3.4. Internal exposures

(150) Even single intakes of ^{137}Cs , ^{131}I , ^{90}Sr , ^{238}Pu , ^{239}Pu , ^{241}Am , and tritium oxide can exert a long-term inhibiting effect on the gonads. Chronic irradiation of female

rats with ^{90}Sr (dose to ovary ~ 1 Gy) leads to a decrease in the number of developing and primordial follicles in the ovaries, and lengthening of the menstrual cycle. In male rats (maximum 0.7–0.8 Gy to the testes), it causes a reduction in the number of spermatocytes, spermatids, and spermatozoa. Shrunken and empty canaliculi, containing nuclei of Sertoli cells and isolated cells of the germinative epithelium, were frequently seen (Shvedov and Akleyev, 2001). The effects exerted by radionuclides on reproductive function are complex and related to both the direct irradiation of the gonads and their effect on the hypophysis and endocrine glands (Dedov and Norets, 1981; Lyaginskaya, 2004).

2.3.5. Summary

(151) Certain developmental cell stages in spermatogenesis are very sensitive to irradiation, causing transient infertility after < 1 Gy. However, fertility recovers from surviving stem cells, even after doses of ≥ 4 Gy. The endocrine regulatory system is much more resistant, and is only injured by high therapeutic radiation doses. The human oocyte is very sensitive to radiation-induced apoptosis, with an estimated LD_{50} of < 2 Gy. This is the cause of radiation-induced infertility, which occurs more often in older women because of the declining oocyte population with age. Also, uterine function may be impaired following high therapeutic radiation doses, and this can affect successful pregnancy.

2.4. Skin

2.4.1. Anatomical features and proliferative organisation

(152) The skin is one of the major organs of the body (Fig. 2.5). In a standard 70-kg man, it has a surface area of approximately 2 m^2 and weighs 2.1 kg, representing 3% of total body weight. It has a highly complex structure designed to serve many vital functions. One major function of the skin is to provide a physical barrier to protect the body against the hazards of the environment, controlling fluid or electrolyte loss in climates that may vary considerably from dry to humid. The skin also has an important role in thermoregulation. Cooling can be achieved by dissipating heat via the surface blood vessels, or by the evaporation of fluid secreted on to the surface of the skin by specialised structures. The layer of subcutaneous fat acts as an insulator for retention of heat. The skin has important sensory functions, senses the external environment, and is an aid to physical and chemical communications. The most recently recognised function of the skin is its role in the body's immune system.

(153) The skin is composed of a series of layers that can be broadly grouped into two structures. The outermost layers are referred to collectively as the epidermis, which is derived from the embryonic ectoderm. The deeper layer, the dermis, is derived from the embryonic mesenchyme. The dermis is infiltrated with specialised structures formed by an infolding of the epidermis, which are collectively referred to as the skin appendages. The salient features of the structure of the skin have

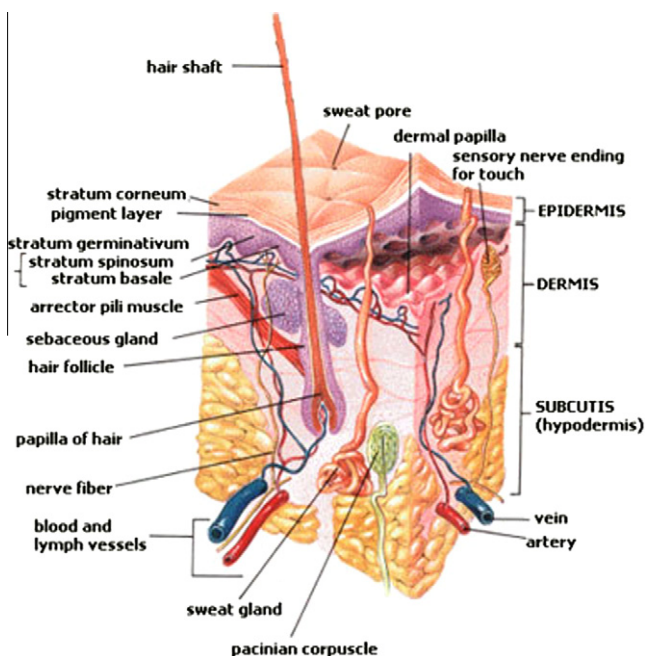


Fig. 2.5. Diagrammatic representation of human skin. Source: <http://training.seer.cancer.gov/melanoma/anatomy/>.

been described elsewhere (ICRP, 1991b), and are summarised here. (a) The epidermis is composed of viable and non-viable layers. The outer layer of dead cells, the stratum corneum, constitutes 25% of the total epidermal thickness. (b) In the viable epidermis, stem cells are restricted to the basal layer, although cell divisions do occur in suprabasal cells. (c) More than 50% of basal cells are found at a depth of $>200\ \mu\text{m}$, distributed in the shaft of hair follicles at varying depths within the dermis. (d) The depth of the basal layer in the interfollicular epidermis varies greatly but is between 20 and $100\ \mu\text{m}$ in most body sites. On the hands, the epidermis of the finger tips is thicker, and the depth of the basal layer is $>160\ \mu\text{m}$. (e) The products of keratinocytes, such as epidermal-cell-derived thymocyte-activating factor and the Langerhans cells that process antigens, make skin an important component of the immune system. (f) The dermis is composed of 75% collagen by dry weight. The collagen is arranged in bundles that intersect at oblique angles to the skin surface, which gives the skin its unique mechanical properties. (g) The thickness of the dermis varies with body site but is usually within the range of 1.0–3.0 mm, approximately 10 times the epidermal thickness in a specific site. (h) The upper papillary dermis is very well vascularised. Approximately 90% of the blood flow is associated with temperature regulation. (i) The vascular supply to the skin of man is predominantly via segmental musculocutaneous arteries, which supply relatively small areas of skin.

2.4.2. Skin reactions after irradiation

(154) Exposure of the skin may lead to the development of several waves of erythema (reddening) of the skin. An early response (early transient erythema) is seen a few hours after doses of >2 Gy, when the exposed area is relatively large. This is related to changes in vascular permeability. The main erythematous reaction, which begins after approximately 10 days, develops as a consequence of the inflammation secondary to the death of epithelial basal cells. A late wave of erythema may also be seen with an onset at approximately 8–10 weeks after exposure. This has a bluish tinge and represents dermal ischaemia.

(155) The reaction of the epidermis to radiation exposure is one of the most extensively documented amongst all tissues (Potten, 1985; ICRP, 1992). The cells at greatest risk are the basal cells of the epidermis; these are gradually lost after irradiation, leading to the development of epidermal hypoplasia within 3–5 weeks of exposure. The severity of clinical changes associated with epidermal hypoplasia depends on the size of the radiation dose. Severe hypoplasia is identified as moist desquamation. Peeling of the skin, at approximately 4–6 weeks after a single exposure, from the start of fractionated irradiation is classical moist desquamation. The timing depends on the turnover time of epidermis in the individual patient, which is usually 4–6 weeks.

(156) In much the same way that radiation produces hypoplasia in the epidermis, it will also inhibit the proliferation of matrix cells in the base of a growing hair. This may be transient, leading to hair thinning, or can produce alopecia or epilation, with the eventual regrowth of hair. However, hair loss may be permanent. Again, like epidermal hypoplasia, this reaction is seen within a few weeks of exposure.

(157) In cases of high-dose exposure, the healing of moist desquamation, which depends on cell proliferation and the migration of viable cells, may only occur very slowly. In these cases, there may be a progressive loss of dermal tissue, referred to as secondary ulceration. Such ulceration can be enlarged significantly if infection supervenes. Secondary radiation-induced ulcers heal slowly, some 6–10 weeks or even longer after exposure, by a process of field contraction and fibrous tissue formation (scarring), as with any burn or excision wound in skin. Radiation exposure may also impair normal wound healing mechanisms that operate after surgery. Changes in vasculature, effects on fibroblasts, and varying levels of regulatory growth factors result in the potential for altered wound healing whether radiation is given before or after surgery. Surgical factors such as incision size, as well as radiation parameters including dose and fractionation, are important parameters in overall treatment strategy (Tibbs, 1997; Dormand et al., 2005; Devalia and Mansfield, 2008). There are examples of radiation effects on wound healing when a single dose of >8 Gy, or its iso-effective fractionated dose, is delivered within 1 month before or after surgery.

(158) If severe and persistent early radiation-induced changes are avoided, a range of late-occurring lesions may still develop. A late phase of erythema is identified by a distinct dusky or mauve ischaemia. This has been well characterised in experimental models (using pigs whose skin closely approximates human skin) after single or fractionated doses of irradiation (Archambeau et al., 1985; Hopewell and Van den Aardweg, 1988). The latency for the development of necrosis is 9–16 weeks

Table 2.2. Approximate threshold single doses and time of onset for the reaction of human skin to ionising radiation delivered in fluoroscopy exposures [ICRP, 2000; based on information in Wagner and Archer (1998) with reference to Hopewell (1986)]. These threshold doses are considered to be near to ED₁ (the estimated dose for 1% incidence).

Effect	Approximate threshold dose (Gy)	Time of onset
Early transient erythema	2	2–24 h
Main erythema reaction	6	≈1.5 weeks
Temporary epilation	3	≈3 weeks
Permanent epilation	7	≈3 weeks
Dry desquamation	14	≈4–6 weeks
Moist desquamation	18	≈4 weeks
Secondary ulceration	24	>6 weeks
Late erythema	15	8–10 weeks
Ischaemic dermal necrosis	18	>10 weeks
Dermal atrophy (first phase)	10	>52 weeks
Telangiectasia	10	>52 weeks
Dermal necrosis (late phase)	>15?	>52 weeks

(Archambeau et al., 1968; Hopewell and Van den Aardweg, 1988; Barabanova and Osanov, 1990). Similar effects will occur after fractionated doses, resulting in a higher cumulative dose to an area of human skin. This is a potential problem if certain diagnostic procedures delivering moderate doses of radiation are repeated or several procedures are undertaken (ICRP, 2000). For early skin reactions (erythema and desquamation), many studies of fractionation sensitivity in both rodents and humans indicate an α/β ratio of approximately 10 Gy (Bentzen and Joiner, 2009; Joiner and Bentzen, 2009) for schedules over several weeks. When short schedules were used, which avoided effects due to incomplete repair and repopulation, the value was lower at approximately 4 Gy (Hopewell et al., 2003).

(159) Late skin changes occur from 26 weeks after irradiation and are characterised by a thinning of dermal tissue, telangiectasia, and the possibility of late necrosis. Dermal thinning has been well documented in pig skin (Hopewell et al., 1979, 1989). Clinically, it is recognised as subcutaneous induration (Gauwerky and Langheim, 1978) and may have been erroneously referred to as subcutaneous fibrosis. Telangiectasia is a repeatedly documented late change in human skin after radiotherapy exposure, and is rarely seen earlier than 52 weeks. It then increases in both incidence and severity for up to at least 10 years after irradiation. The rate of progression of telangiectasia is dose related (Turesson and Notter, 1984). Late necrosis may be promoted by trauma, or other factors, at any time.

(160) A summary of approximate threshold doses and times of onset for the reaction of the skin to ionising radiation is given in Table 2.2. These skin changes are largely avoided in modern radiotherapy which uses penetrating beams of radiation, providing dose sparing in the skin.

2.4.3. Dose–effect relationships and threshold doses

(161) It has been a long-accepted practice in radiotherapy to reduce the total dose to skin as the treatment area is increased (ICRP, 1991b). Based on clinical experience

with orthovoltage x rays, several authors (Ellis, 1942; Paterson, 1948) proposed safe ‘tolerance’ doses for human skin. The doses proposed were in broad agreement with each other, but the biological basis of the term ‘clinical tolerance’ was not clearly defined. Ellis (1942) provided some broad guidelines: small fields were said to tolerate the occurrence of moist desquamation which was associated with prompt healing, whilst large fields only tolerated a dose that produced dry desquamation (moist desquamation was said to be unacceptable over a larger area). Considerable confusion was caused when these clinically derived ‘tolerance doses’ were accepted as iso-effective doses for the skin by authors proposing mathematical formulae for area-effect and volume-effect relationships for the skin (Von Essen, 1948).

(162) Human data that have established a dose-effect relationship for late skin damage have come from studies on patients receiving fractionated radiotherapy treatment. Examination of the incidence of clinically evident late atrophy in large fields suggested that the total dose given in 30 fractions that was associated with a 50% incidence of a visible effect (ED_{50}) was approximately 69 Gy (Hopewell et al., 1989). These fractionated radiation doses can be used to calculate equivalent acute single doses by using an LQ equation (see Section 1.3.1). Assuming an α/β ratio of 3 Gy for late damage to the skin, the equivalent single doses, based on these data, would be approximately 17 Gy for ED_{50} and 10.5 Gy for ED_1 . For late telangiectasia in human skin, ED_{50} for a moderate severity of telangiectasia at 5 years was approximately 65 Gy for fractionated doses given as 2 Gy/fraction with five fractions/week (Turesson and Notter, 1984, 1986), and ED_1 was approximately 40 Gy.

(163) Clinical experience, based on studies of human skin in patients receiving radiotherapy treatment, has suggested that there may be both age- and body-site-related differences in radiosensitivity. However, these differences are relatively small; for example, in patients showing skin with an aged or weathered appearance, a reduction in dose of up to 10% will be made in some treatment centres. There is no evidence to suggest that the sex of a patient has any influence on the radiosensitivity of the skin.

(164) In an experimental study in the pig, no field-size effect could be demonstrated when the responses of 4×4 cm and 4×16 cm skin fields were compared (Hopewell and Young, 1982). In experiments related to radiological protection (Hopewell et al., 1986), circular areas of pig skin, 5–40 mm in diameter, were irradiated with $^{90}\text{Sr}/^{90}\text{Y}$. ED_{50} values for moist desquamation were derived from the dose-effect curves for the incidence of moist desquamation against dose, where the doses represented the central axis dose at 16- μm depth over an area of 1.1 mm². ED_{50} values were found to decline markedly from approximately 70 Gy for a source with a diameter of 5 mm to approximately 27 Gy for a source with a diameter of ≥ 22.5 mm. The sparing effect seen for irradiation of very small volumes was attributed to migration of cells from outside the irradiated area. Irradiated areas with a diameter of 15 mm would appear to be the upper limit at which cell migration from the edges of the irradiated area had a significant influence. There was no change in ED_{50} for sources with a diameter of 22.5 and 40 mm. The dose-effect curves for the sources with diameters of 5, 11, and 15 mm had a significantly more shallow slope than those for the two large sources, implying a greater inhomogeneity in the cell populations irradiated with the smaller

sources, and possibly reflecting an increase in the stimulus for cell migration after higher doses.

(165) The irradiation of skin with a beta-ray emitter of significantly lower energy than $^{90}\text{Sr}/^{90}\text{Y}$ (e.g. ^{170}Tm , E_{max} (maximum energy) 0.97 MeV) would leave many reproductively viable basal cells within the irradiated area (i.e. those basal cells situated in the hair follicle canal). In such a situation, cell migration from the edges of an irradiated area would be expected to be of reduced significance in determining the response of areas of increasing size to irradiation. The finding of a significantly reduced field-size effect and higher skin-surface doses for ED_{50} , ED_{10} , and ED_1 in pig skin after irradiation with ^{170}Tm sources with a diameter of 5–19 mm provides major evidence for the presence and importance of viable clonogenic cells within the hair follicle canal.

(166) A comparison of the radiation responses of the skin to $^{90}\text{Sr}/^{90}\text{Y}$ and ^{170}Tm with that of ^{147}Pm ($E_{\text{max}} \sim 0.25$ MeV, range <0.5 mm) is not entirely meaningful because of the change in the biological response produced by very-low-energy beta-ray emitters. With low-energy beta emitters such as ^{147}Pm , for which the beta particles barely penetrate the superficial dermis, only minimal erythema in the skin is produced, even up to high skin surface doses of ~ 100 Gy.

(167) After very high doses, a unique response, referred to as 'acute epidermal necrosis', can be produced because of the direct interphase death of postmitotic cells above the basal layer of the epidermis. This effect is similar in macroscopic appearance to classical moist desquamation induced by more penetrating radiations, but it occurs much earlier (within approximately 10 days) and lasts for a very short period. The dose-effect curves for acute epithelial necrosis after ^{147}Pm showed a small field-size effect, but this is of doubtful significance because of the difficulties associated with the recognition of minor skin changes in very small areas. Estimated threshold doses for several beta emitters regarding acute epidermal necrosis in pigs have been reported (Table 5 in ICRP, 1991b). Low-energy beta radiations do not produce any of the more severe skin responses that can be produced by high-energy beta emitters (e.g. ^{90}Y , E_{max} 2.3 MeV, range ~ 9 mm), which can penetrate well into the dermis.

(168) For intermediate- and higher-energy beta-ray emitters, dermal atrophy and damage to the deep vasculature, including telangiectasia, are the main late effects following an acute exposure. They become apparent over a time scale of months or years. Dermal atrophy, detected as dermal thinning or as induration of the skin, has a target depth of approximately 0.3–0.5 mm, and a threshold single dose (in pigs) of approximately 10 Gy. Measurements of dermal thickness at 2 years after the irradiation of pig skin showed that significant dermal thinning was observed at doses that did not produce early epithelial desquamation or acute ulceration in the case of sources with a diameter of 2 mm (Hamlet et al., 1986). However, threshold doses for the atrophy of the skin have still to be established for a severity of dermal thinning that might be considered to be cosmetically unacceptable.

(169) Dermal necrosis results from damage to the deep dermal vasculature, and occurs 10–15 weeks after exposure. The target depth is >1 mm, and hence low-energy beta rays do not produce this effect. Dermal necrosis was observed in some

of the Chernobyl accident victims who received absorbed doses of 2–20 Gy from high-energy beta radiation, quoted at a depth of 1.5 mm (Barabanova and Osanov, 1990). From the above information, it is clear that threshold doses for particular endpoints with beta radiation types of different ranges need to be qualified by the depth at which they are quoted. This aspect and consideration of exposure of different skin sites, such as hands and feet, are discussed in further detail in *Publication 59* (ICRP, 1991b).

(170) A factor with a major effect on the radiosensitivity of the skin is the LET of the radiation. The RBE increases with decreasing neutron energy. For very small doses/fraction, the RBE ranged from 3 to 4 for high-energy fast neutrons (42 MeV_{d+Be} or 62 MeV_{p+Be}) to approximately 8 for low-energy fast neutrons (4 MeV_{d+Be}). RBE values in the range of 1.5–4.0 are applicable for large single doses of ≥ 10 Gy (Hopewell et al., 1988; Joiner and Field, 1988).

2.4.4. Protraction of exposure

(171) The dose–response relationships for both early and late radiation-induced damage to the skin are significantly influenced by the exposure rate. For acute radiation exposures, the dose limit should be based on the response of the dermis in order to prevent the development of what might be considered detrimental late effects, such as dermal atrophy or telangiectasia. Protraction of the dose over a period of 1–3 weeks, either by irradiation at low dose rates or by using multiple small dose fractions, results in a higher ED₁ for both early and late radiation-induced injury. Since repopulation by epithelial cells would not be significant over this period (Turesson and Notter, 1984; Van den Aardweg et al., 1988), the sparing of the dose is mainly due to the repair of sublethal injury from low-LET radiation. The repair capacity of the dermal vascular/connective tissues is greater than that of the epidermis, and hence the response of the dermis will be reduced relative to that of the epidermis.

(172) For the late dermal changes, where the α/β ratio is approximately 3 Gy, there is considerable uncertainty about the significance of a time factor, which might be associated with cellular repopulation. Therefore, it is uncertain how late dermal effects might be modified by extended protraction of the dose, beyond what is known from the results of studies on patients receiving radiation therapy. In the light of this uncertainty, ED₁ of approximately 40 Gy for telangiectasia and late atrophy obtained for human skin after irradiation with 2-Gy fractions would appear to be the most appropriate for radiological protection if late effects of this type are to be avoided.

(173) Simple split-dose studies in the pig, using two equal doses, have suggested that full recovery of the epidermis is completed with a 6-week interval between doses (Van den Aardweg et al., 1988). However, after daily (five per week) fractionation over 6 weeks, full recovery may be delayed until at least 2 weeks after the completion of irradiation (Morris and Hopewell, 1986). Clearly, with extensive protraction of the dose, the epidermis will be spared considerably due to repopulation, and thus the late dermal changes will again predominate.

(174) Effects of total skin irradiation have been observed in several series of patients treated for mycosis fungoides. For example, patients who received two total skin doses of 2 Gy/week with a total dose of up to 36 Gy over a protracted period of 9 weeks showed various degrees of skin reactions after delivery of 20 Gy (Desai et al., 1988).

(175) A cutaneous radiation syndrome has been described (Peter, 1996), observed in particular after the Chernobyl accident (Gottlöber et al., 2001). In 16 of the 28 individuals who died from the immediate consequences of accidental radiation exposure, the primary cause was attributed to cutaneous radiation syndrome. Estimated total-body doses ranged from 2.1 to 9 Gy, and skin doses were considerably higher. The early signs of cutaneous radiation syndrome range from erythema to blisters, exfoliations and ulcerations of the skin, alopecia, mucositis, and conjunctivitis. The late signs include xerosis, cutaneous telangiectasias, subungual splinter haemorrhages, epidermal atrophy, disseminated keratoses, dermal and subcutaneous fibrosis with partial ulcerations, and pigmentary changes including radiation lentigo.

2.4.5. Summary

(176) The skin demonstrates both early and late reactions after irradiation. Early reactions, which occur hours to weeks after exposure, include erythema, epilation, and desquamation. Late reactions, which occur months to years after irradiation, include dermal erythematous reactions, atrophy, induration, telangiectasia, necrosis, and fibrosis. Both early and late reactions show an area effect, with smaller areas tolerating larger doses because of migration of unirradiated cells into the irradiated area. Late reactions show a greater sparing effect of dose fractionation than early reactions, except in the case of late reactions consequential to severe early reactions. Early reactions are spared by dose protraction because of repopulation of epidermal stem cells during the protracted irradiation. Late reactions show very little sparing from dose protraction because of the lack of any contribution from cell repopulation, which is the explanation for early-reaction sparing. Regarding radiation protection for protracted or chronic irradiation scenarios, the epidermis will be spared considerably due to repopulation, and thus the threshold doses will pertain predominantly to late dermal changes.

2.5. Cardiovascular and cerebrovascular systems

2.5.1. Anatomical features and proliferative organisation

(177) The heart is a four-chambered muscular pump consisting of two atria and two ventricles. A single layer of flattened epithelial cells (the mesothelium) covers the outer layer of the heart (epicardium). Outside this layer is another fibroelastic membrane lined with mesothelium, the pericardium. Between the two mesothelial layers is the pericardial cavity, with a thin film of fluid that permits the heart to move

freely during contraction and relaxation. A layer of fibrous connective tissue and adipose tissue separates the epicardium from the underlying muscular myocardium (comprising myocytes, fibroblasts, smooth muscle cells, capillaries, and nerves) and the inner endothelial layer (endocardium). Large coronary arteries on the surface of the heart supply the epicardium, and smaller arteries, branching into arterioles and capillaries, feed the myocardium.

(178) All arteries have three layers: the intima (in contact with the vessel lumen), the media, and the outermost adventitia. The intima is composed of a smooth layer of endothelial cells on a delicate basement membrane that penetrates between the subendothelial connective tissue and the underlying smooth muscle cells. The media consists of smooth muscle cells and an elastic network. The adventitia is a poorly defined layer of connective tissue in which elastic and nerve fibres and – in large arteries – small, thin-walled nutrient vessels are dispersed. The three separate layers seen in arteries are not well defined in veins. In general, veins are thin walled with relatively large lumina.

(179) The valves between the atria and ventricles prevent backflow of blood from the ventricles to the atria during systole. In addition, the valves between the heart and the aorta, and the heart and the pulmonary arteries prevent backflow from the aorta and the pulmonary arteries, respectively, into the ventricles during diastole. The heart valves do not have a blood supply but they are covered with a specific type of endothelium.

(180) Cardiac contraction is generated by the myocytes. Myocytes are highly differentiated mononuclear cells rich in mitochondria. Adjacent myocytes are separated by intercalated discs, and they form a network of branching fibres with the ability to carry forward an action potential. Myocytes contract spontaneously and continuously under the regulation of electrical impulses. The electrical impulse initiates in the sinoatrial node (pacemaker) at the junction between the right atrium and the superior vena cava, and is propagated to the atrioventricular node, located between the atria and the ventricles. The distal part of the atrioventricular node, the bundle of His, splits into two branches to activate the left and right ventricle, respectively. Noradrenaline and its receptors regulate heart rate and the force of contraction.

(181) The normal adult heart is a slow turnover organ, with very low proliferative activity in its constituent cell types. Indeed, it was previously thought that cardiomyocytes were terminally differentiated, without the capacity for cell division. It was assumed that loss of myocytes as a result of injury or ageing was compensated by hypertrophy of remaining myocytes or by fibrosis. However, recent studies have identified a pool of stem cells and progenitor cells that can generate myocytes, smooth muscle cells, and endothelial cells, and participate in regeneration of the adult heart (Anversa et al., 2007). New evidence has also shown that circulating mononuclear cells, including progenitor endothelial cells, can home to sites of ischaemic damage in the heart, and contribute to new vessel formation by transdifferentiation into endothelial cells and secretion of angiogenic cytokines (Caplice and Doyle, 2005).

2.5.2. Radiation exposure at doses of <5 Gy

(182) Circulatory diseases are major causes of disability and mortality, accounting for 30–50% of all deaths in most developed countries. Coronary artery and cerebrovascular diseases are late manifestations of atherosclerotic changes of the arteries, and represent the principal causes of vascular disease mortality and morbidity in many populations. These are multifactorial diseases involving smoking, diet, and other lifestyle and personal factors. It is currently thought that initial endothelial injury is induced by endotoxins, hypoxia, infection, or other insults, and that subsequent haemodynamic disturbances, inflammatory mechanisms, and effects of hyperlipidaemia are the most important factors leading to atherosclerotic plaque (Lusis, 2000; Libby, 2002).

(183) Epidemiological data on circulatory diseases associated with exposure to radiation at low doses require careful assessment to distinguish causal relationships between radiation and the disease from those due to confounding factors. Establishing a dose–response relationship can be helpful in identifying a causal relationship in observational studies. These can best be achieved in large exposed populations, in which cardiovascular endpoints are well established and for which information on major risk factors is available. In reality, such opportunities are rare. However, if several studies of different populations, with different exposure scenarios and different study methods, show consistently similar results, this provides credibility to the causal association. Consideration of confounding factors is important since the magnitude of cardiovascular disease risk from low-dose radiation exposure is small relative to the effects of other environmental, lifestyle, and personal risk factors. It should be cautioned that small cohorts are often underpowered for identification of significant risks (Land, 1980). In large observational studies, associations may still be due to confounding factors or selection bias, especially for simple comparisons of exposed vs unexposed groups.

(184) Concern for an increased risk of cardiovascular disease risk from low-dose radiation first arose from data on non-cancer diseases from the Japanese atomic bomb survivors, who received single whole-body exposure to a range of doses of <5 Gy (Shimizu et al., 1999). To examine the association between low-dose radiation and non-cancer diseases, especially circulatory disease, in other irradiated populations, UNSCEAR (2006) identified >30 potentially informative cohort studies. These included patients irradiated for the treatment of benign diseases with fractionated and localised exposure at <5–6 Gy (cumulative dose), people irradiated repeatedly for diagnostic radiation at <1 Gy (cumulative dose), and people with chronic occupational exposure, mostly whole-body doses of <0.5 Gy (cumulative dose). Mortality or morbidity data on cardiovascular disease were available from >20 of these studies, but only 10 studies evaluated the dose–response relationship for cardiovascular disease (UNSCEAR, 2006). Separately, McGale and Darby carried out systematic reviews of the published epidemiological literature on cardiovascular disease (McGale and Darby, 2005, 2008). Several other reviews of studies of populations exposed medically, occupationally, or environmentally to relatively low-dose radiation have been published (Little et al., 2008, 2010; Metz-Flamant et al., 2009;

Table 2.3. Published epidemiological studies on the risk of circulatory disease (cardiovascular and cerebrovascular) associated with low linear energy transfer radiation doses of <5 Gy, based upon Little et al. (2010) and subsequent publications.

Population	Association between circulatory disease and radiation exposure	
	Cardiovascular	Cerebrovascular
<p><i>Studies reporting a significant positive radiation effect</i></p> <p>Life Span Study, atomic bomb survivors (Yamada et al., 2004; Shimizu et al., 2010)</p> <p>Radiological technologists, USA (Hauptmann et al., 2003)</p> <p>Patients irradiated for peptic ulcer, USA (Carr et al., 2005)</p> <p>Chernobyl accident emergency workers, Russia (Ivanov et al., 2006)</p> <p>British Nuclear Fuels workers, UK (McGeoghegan et al., 2008)</p> <p>Radiologists, USA (Matanoski et al., 1964)</p> <p>Mayak, Russian Federation (Azizova et al., 2010a)</p>	<p>Mean dose (range)*</p> <p>Colon: 0.15 Gy (0-4)</p> <p>Heart: 0.01 Gy (0-0.46)</p> <p>Heart: 1.3 Gy (0-7.6); carotid: quartile mean, range 0.1-0.24 Gy</p> <p>0.109 Gy</p> <p>0.53 Sv (99th%, 0.589)</p> <p>Radiologists dying, 1950-1954: 8-20 Sv lifetime</p> <p>External γ: 0.91 Gy (males); 0.65 Gy (females)</p> <p>α Pu: 0.40 Gy (males); 0.81 Gy (females)</p>	<p>Cerebrovascular mortality, 1950-2003: ERR/Gy = 0.09 (95% CI -0.01 to 0.17)</p> <p>Stroke incidence, 1958-1998: ERR/Gy = 0.07 (95% CI -0.08 to 0.24)</p> <p>RR = 2.40 (first worked <1940); 1.54 (1940-1949); 0.90 (1950-1959); 1.00 (\geq 1960)</p> <p>RR = 1.36 (lowest quartile); 0.99; 0.98; 0.82 (highest category)</p> <p>Cerebrovascular morbidity: ERR/Gy = 0.45 (95% CI 0.11-0.80)</p> <p>Cerebrovascular mortality: ERR/Sv = 0.43 (95% CI -0.10 to 1.12)</p> <p>SMR (arteriosclerosis: heart disease) = 1.03 (radiologists, 1920-1939); 1.15 (1940-1969)</p> <p>IHD, external γ dose ERR/Gy: Incidence: 0.11 (95% CI 0.05-0.17)</p> <p>Mortality: 0.07 (95% CI -0.02 to 0.15)</p> <p>Cerebrovascular disease, external γ dose ERR/Gy: Incidence: 0.46 (95% CI 0.36-0.57)</p> <p>Mortality: -0.02 (95% CI -0.12 to 0.07)</p>

Early and Late Effects of Radiation in Normal Tissues and Organs

Table 2.3. (continued)

Population	Association between circulatory disease and radiation exposure	
	Mean dose (range)*	Cardiovascular
<i>Studies not reporting a significant positive radiation effect</i>		
Tuberculosis patients, USA (Davis et al., 1989)	Lifetime exposure 20 Sv (1897-1920) 3.8 Sv (1921-1935)	Mortality from all circulatory diseases: ERR/Gy = -0.11 (95% CI -0.20 to -0.01)
Radiologists, UK (Berrington et al., 2001)	Heart: 2.49 Gy (0.0-17.28) Brain: 0.14 Gy (0.0-4.80)	RR vs other medical practitioners (all circulatory disease) = 1.30 Radiologists registered 1897-1920 = 1.15 Radiologists registered 1920-1935 = 0.84 Radiologists registered 1936-1954 = 0.69 Radiologists registered 1955-1979
Patients with ankylosing spondylitis (Darby et al., 1987, 2005)	Cumulative recorded: 0.0207 Sv (0->0.5 Sv)	Mortality from circulatory disease, excluding stroke: RR = 0.97 (exposed vs unexposed), ns ERR/Gy = -0.01 (95% CI -0.12 to 0.13)
IARC 15-country nuclear workers (Wilheid et al., 2007a)	Cumulative recorded: 0.0215 Sv (0->0.2 Sv)	Circulatory disease mortality: ERR/Sv = 0.09 (95% CI -0.43 to 0.70) IHD mortality: ERR = -0.01 (95% CI -0.59 to 0.69)
French Nuclear Workers Study (Laurent et al., 2010)	Cumulative recorded: 0.025 Sv	RR at 0.1 Sv Circulatory disease mortality: 1.27 (90% CI 0.77-1.91) IHD mortality: 1.41 (90% CI 0.71-2.37)
National Registry for Radiation Workers, UK (Muirhead et al., 2009)	0.025 Sv	Circulatory disease mortality: ERR/Sv = 0.25 (95% CI -0.01 to 0.54) IHD: ERR/Sv = 0.26 (95% CI -0.05 to 0.61)
German uranium miners (Kreuzer et al., 2006)	0.041 Sv (0->0.3 Sv), external gamma dose	Heart disease mortality, external γ dose: ERR/Sv = -0.35 (95% CI -0.7 to 0.009) Cerebrovascular, external γ dose: ERR/Sv = 0.09 (95% CI -0.6 to 0.8)

IHD, ischaemic heart disease; IARC, International Agency for Research on Cancer; ERR, excess relative risk; SMR, standardised mortality ratio; RR, relative risk; CI, confidence interval; ns, not significant.

* The atomic bomb survivor studies use dose estimates in terms of weighted colon dose in Gy, which is the sum of gamma dose estimates and 10 times neutron dose estimates. In some other studies, weighted dose estimates are provided in Sv, as reported by the authors.

Darby et al., 2010). These reviews generally agree that there is substantial heterogeneity between studies in the observed associations between radiation exposure and circulatory disease, either cardiovascular or cerebrovascular. The large heterogeneity in the risk per unit radiation dose is reduced by adjustment of the effects of dose fractionation, but remains significant, possibly resulting from confounding or bias (Little et al., 2010). Further relevant study results, discussed below, are summarised in Table 2.3.

Atomic bomb survivors

(185) Mortality data from the Life Span Study of the Japanese atomic bomb survivors provide evidence of a dose response for mortality from heart disease, cerebrovascular disease, and other non-cancer diseases (respiratory and digestive diseases) (Shimizu et al., 1999; Preston et al., 2003). Approximately 60% of radiation-related excess non-cancer deaths are from circulatory disease. The most recent analysis of heart disease and cerebrovascular disease mortality in the Life Span Study was based on follow-up over the period 1950–2003 (Shimizu et al., 2010) (see Fig. 2.6).

(186) Although Shimizu et al. (2010) referred to ‘stroke’ in their analyses of International Classification of Diseases, Ninth Revision (ICD9) 430–438, ‘cerebrovascular disease’ is referred to here because stroke is usually defined as a subset of these ICD codes. For cerebrovascular disease (ICD9 codes: 430–438), there were approximately 9600 deaths and the estimated excess relative risk per Gy (ERR/Gy) was 9% [95% confidence interval (CI) 1–17%, $P = 0.02$] based on a linear dose–response model. There were approximately 8400 deaths from heart disease as a whole (ICD9 codes: 390–398, 402, 404, 410–429). This is lower than the value that would be expected for populations in Europe and North America, reflecting differences between populations in genetic factors and/or lifestyle factors, such as smoking and diet. The ERR/Gy for heart disease overall was 14% (95% CI 6–23%, $P < 0.001$); a linear model provided the best fit to these data. However, the dose–response relationship over the restricted dose range of 0–0.5 Gy was not significant, whereas the corresponding dose–response relationship over 0–1 Gy was significant. Analyses of dose–response thresholds yielded maximum likelihood doses of 0 Gy (95% CI <0–0.5 Gy) for heart disease and 0.5 Gy (95% CI <0–2 Gy) for cerebrovascular disease. Based on an autopsy vs death certificate comparison, the broader diagnostic categories of all heart disease and all cerebrovascular disease were relatively accurate (92% and 86% confirmed, respectively). However, the authors noted substantial misclassification of subtypes of heart disease on death certificate diagnoses, such that limited meaning could be attached to the results of the analyses of various subtypes of cardiovascular disease. With that caveat, analyses specific to various types of heart disease found that the evidence for an association was greatest for hypertensive heart disease, rheumatic heart disease, and heart failure. For ischaemic heart disease, which has been the focus of investigation in other studies of radiation and cardiovascular disease, the ERR/Gy was 0.02 (95% CI –0.10 to 0.15). There was also no evidence of an association with radiation for myocardial infarction (ERR/Gy = 0, 95% CI –0.15 to 0.18).

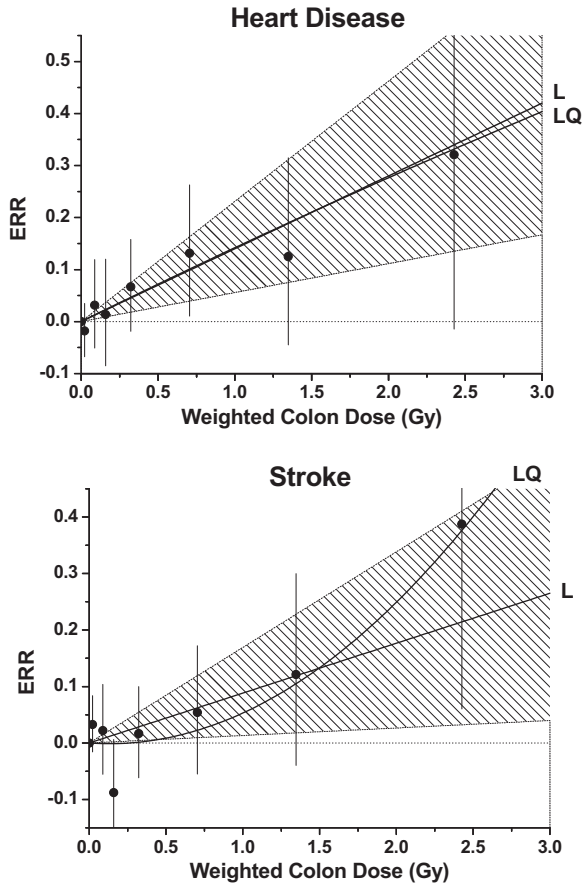


Fig. 2.6. Radiation dose–response relationship, excess relative risk (ERR) for heart disease and cerebrovascular disease mortality, showing the linear (L) and linear-quadratic functions (LQ). Weighted colon dose in Gy is the sum of gamma dose estimate and 10 times neutron dose estimate (Shimizu et al., 2010).

(187) Several potential sources of bias and confounding factors were considered in the study of heart disease and cerebrovascular disease among atomic bomb survivors (Shimizu et al., 2010). The effects considered included: possible misclassification of causes of death, particularly cancer, that may cause a spurious association between heart disease or cerebrovascular disease mortality and radiation dose; and the possibility that radiation dose, which is closely correlated with the distance from the hypocentre, may be confounded by smoking, alcohol intake, education, occupation, obesity, or diabetes that may affect circulatory disease rates (Shimizu et al., 2010). None of the potential biases or confounders significantly altered the dose–response relationship for heart disease or cerebrovascular disease mortality. Specifically, statistical adjustment for smoking and other risk factors increased the ERR/Gy for

heart disease by only 0.001 and decreased it for cerebrovascular disease by only 0.009.

(188) Analysis of mortality over 1950–2003 in the Life Span Study showed no significant variation by attained age, age at exposure, or gender in the ERR/Gy for cerebrovascular disease or for heart disease taken as a whole (Shimizu et al., 2010). There was a suggestion that the ERR/Gy for cerebrovascular disease might be higher before 60 years of age than after, especially among men, but the interpretation of this subgroup analysis is limited. There was also a non-significant indication of an age at exposure effect for cerebrovascular disease (ERR/Gy = 0.36, 0.09, 0.15, and 0.05 for ages <10, 10–19, 20–39, and \geq 40 years at exposure, respectively).

(189) A significant dose–response relationship was also found in a study of 288 incident cases of myocardial infarction in the clinical (Adult Health Study) subset of the Life Span Study cohort (Kodama et al., 1996). The relative risk (RR) at 1 Gy was estimated to be 1.17 (95% CI 1.01–1.36). The association between myocardial infarction and radiation dose remained significant after adjusting for blood pressure and serum cholesterol levels, as well as age and gender. A more recent analysis (Yamada et al., 2004) reported an insignificantly elevated RR for the incidence and prevalence of heart disease in the participants in the Adult Health Study (1.05 at 1 Sv, 95% CI 0.95–1.16). However, there is potential survivor/selection bias involved in prevalence cases.

(190) Clinical laboratory data from the clinical Adult Health Study subset also provide some insight into subclinical changes underlying disease development. Analyses of biennial health examination data showed a small but significant effect of radiation exposure on the amount of aortic arch calcification (Yamada et al., 2005), and on dose-dependent increases in longitudinal trends for systolic and diastolic blood pressure (Sasaki et al., 2002) and serum cholesterol levels (Wong et al., 1999). There was also a significant dose-related increase in serum levels of various inflammatory markers among the cohort subjects, including C-reactive protein, IL-6, and sialic acid (Neriishi et al., 2001; Hayashi et al., 2003). Elevated C-reactive protein and IL-6 levels were associated with decreases in the proportion of CD4+ T cells in the peripheral blood lymphocytes (Hayashi et al., 2003), suggesting a role of radiation-induced impairment of cell-mediated immunity in the promotion of preclinical inflammation.

Medical exposures

(191) Observational studies of populations irradiated for treatment of non-malignant diseases can provide information on the risk of cardiovascular disease associated with exposure to fractionated doses of <5 Gy. It is necessary, however, to consider the confounding effect of non-malignant diseases for which radiation treatment was given, and also the reasons why patients were treated with radiation rather than other means, such as surgery. For example, thyroid disease may predispose to an increased risk of cardiovascular disease because of altered levels of thyroid hormones. Women given ovarian irradiation for uterine bleeding or other gynaecological disorders were probably in a hyperoestrogenic state, which itself would increase the risk of cardiovascular disease, but this may be offset by lowered

oestrogen levels after killing ovarian cells with radiation. Results of follow-up studies of these populations are therefore difficult to interpret and these are not included in this review.

(192) Patients with ankylosing spondylitis irradiated in the 1930s–1950s received a mean cardiac dose of 2.5 Gy (Lewis et al., 1988). The observed numbers of deaths from cerebrovascular and other circulatory diseases (including heart disease) were higher in this cohort than expected from the general population, but were not higher than expected from another group of unirradiated spondylitis patients (Darby et al., 2005; McGale and Darby, 2005). Among patients with tuberculosis exposed to fluoroscopic radiation, the risk of mortality due to circulatory disease (including both heart and cerebrovascular diseases) was not elevated compared with unirradiated patients with tuberculosis (Davis et al., 1987). Fluoroscopic examination resulted in an accumulated dose of 0.91 Gy in the lung, and doses to the brain were much lower. No dose–response analyses were performed in either of these studies.

(193) A significant dose–response relationship for circulatory disease mortality was reported from a study of women irradiated for scoliosis (mean lung dose of 0.041 Gy), but details were not published (Morin Doody et al., 2000). More detailed dose–response analysis in relation to medical exposure comes from analysis of 10-year survivors of patients irradiated for peptic ulcer disease, which showed a significant dose–response relationship with coronary heart disease for doses of 1.6–3.9 Gy to the entire heart, or 7–18 Gy (in 1.5-Gy fractions) to 5% of the heart that was in the radiation field (Carr et al., 2005). There was no association between the carotid radiation dose and cerebrovascular disease, but the doses to the carotid artery were only approximately 10% of those to the heart. The uneven distribution of radiation doses to the heart (high doses in a small portion of the organ and low doses in the remaining part of the organ) complicates the interpretation of these data, especially for low-dose effects.

(194) Repeated radiological diagnostic or intervention procedures can lead to significant radiation exposure, and the use of such procedures is increasing. In 2006, the per-capita dose from medical exposure (not including dental or radiotherapy) in the USA was approximately 0.003 Sv. These exposures were mainly from computer tomography (CT) scans, as well as angiography and vascular interventions. A single chest CT scan gives an exposure of approximately 0.007 Sv, and cardiac stress tests give 0.01–0.03 Sv. Some complex interventional procedures can deliver substantial accumulated doses to the heart (Schlattel et al., 2007; Matsubara et al., 2011). To date, there are no published studies to evaluate attributable risks for non-cancer diseases to such diagnostic exposures.

Occupational exposures

(195) Radiologists and other medical radiation workers in the early part of the 20th Century received much higher doses of radiation than those employed more recently. Informal estimates are that the radiologists in the 1920s could have been exposed to 100 roentgens/year, and that they may have received annual exposures of 0.1 Sv before the 1950s and approximately 0.05 Sv in the early 1950s. The average

lifetime dose was estimated to be 20 Sv in radiologists who were registered between 1897 and 1920, 3.8 Sv in radiologists registered between 1921 and 1935, 1.25 Sv in radiologists registered between 1936 and 1954, and 0.1 Sv in radiologists registered between 1955 and 1979 (Braestrup, 1957; Smith and Doll, 1981; Berrington et al., 2001). For US radiologists who died between 1930 and 1954, the estimated lifetime (40-year) cumulative doses range from 8 to 20 Sv (BEIR, 1972). These dose estimates, naturally very crude, give some idea of the extent of exposure among early radiologists in general, but not individual variation. Studies of UK and US radiologists provide conflicting results regarding the risk of mortality due to circulatory or heart disease among early radiologists compared with other medical professions (Matanoski et al., 1984; Berrington et al., 2001). Individual dose estimates are lacking in these studies; therefore, quantitative risk estimates are not possible. Among US radiological technologists, heart and cerebrovascular disease mortality was increased among early workers (Hauptmann et al., 2003). This is one of the few studies that controlled for the effects of smoking and other confounders, but radiation dose estimates are not available at the time of reporting.

(196) Analyses of studies of nuclear workers can provide direct estimates of risks at the lowest dose range (<0.5 Gy) based on cumulative measured doses. When data are pooled internationally, this strengthens statistical power but does not eliminate confounding. The limited availability of information on smoking and other possible confounding factors becomes a substantial problem when the radiation-related risk from radiation is small relative to the effects of many other risk factors, as in the case of cardiovascular diseases. The latest international pooled analysis of non-cancer mortality data involved 275,000 nuclear industry workers monitored for external radiation exposure, assembled from cohorts in 15 countries. Workers with potentially high internal exposures and those with exceptionally high annual on-site doses (≥ 0.25 Sv) were excluded from this analysis (Vrijheid et al., 2007b). The ERR/Sv for circulatory disease (including ischaemic heart disease), adjusted for socio-economic status, was 0.09 (95% CI -0.43 to 0.70) (Vrijheid et al., 2007a). This was not significantly elevated, but risks of the same order of magnitude as estimated from the atomic bomb survivor data could not be ruled out.

(197) Another pooled analysis involved approximately 42,000 employees with external and internal radiation exposures at British Nuclear Fuels plc (virtually all of the workers with external radiation alone were also included in the above 15-country study, but with a shorter follow-up period). In analyses that were restricted to males (who constituted $>90\%$ of this cohort), there was a significant dose-response relationship (cumulative external dose) for mortality from circulatory disease (ERR/Sv = 0.65, 90% CI 0.36–0.98) and ischaemic heart disease (ERR/Sv = 0.70, 90% CI 0.33–1.11) (McGeoghegan et al., 2008). The ERR/Sv for cerebrovascular disease tended to be elevated (0.43, 90% CI -0.10 to 1.12), but this was not significant. There was significant heterogeneity in the dose-response relationship for different categories of employment and radiation exposure (internal vs external), which remained unexplained and prevented the authors from making a causal interpretation.

(198) A subsequent analysis of a larger cohort of approximately 175,000 radiation workers in the UK, including virtually all of the workers in the study of McGeoghegan et al. (2008), found some evidence of an association between whole-body dose and mortality from circulatory disease as a whole (ERR/Sv = 0.25, 90% CI 0.03–0.49, 95% CI –0.01 to 0.54) and from ischaemic heart disease in particular (ERR/Sv = 0.26, 90% CI 0.00–0.55, 95% CI –0.05 to 0.61) (Muirhead et al., 2009).

(199) The recent analysis of mortality in a cohort of 22,393 French nuclear workers, who were also included in the 15-country study but with a shorter follow-up period, showed no significant increase in the RR, at 0.1 Sv, of death from circulatory disease in general or from ischaemic heart disease. There was an increased risk of cerebrovascular disease (RR 2.74, 90% CI 1.02–5039), but this estimate was only based on 22 cases. The mean cumulative dose for the whole population was 0.215 Sv, although <5% had received doses of >0.1 Sv (Laurent et al., 2010).

(200) The limited information relating to confounders, particularly lifestyle and environmental factors, is a problem in many of the worker studies. However, some studies show no trends for increases in other non-malignant diseases associated with smoking being related to radiation dose (Vrijheid et al., 2007a; Muirhead et al., 2009; Laurent et al., 2010). This suggests that smoking is unlikely to markedly confound the dose–response relationship for circulatory disease in these studies. Conversely, the significant trend between diabetes and dose in the study of McGeoghegan et al. (2008) suggests that lifestyle factors other than smoking may confound the ischaemic heart disease dose response in this study.

(201) Circulatory disease mortality and incidence have been studied in a cohort of approximately 12,000 workers at the nuclear plants of the Mayak Production Association in the Urals region of Russia. Many of these workers, who were first employed at these plants in 1948–1958, received prolonged exposures from gamma radiation and/or plutonium intakes, often far in excess of current-day radiation protection guidelines. Another notable feature of this study, in contrast to many other studies, was the availability of incidence data, collected on a regular basis whilst workers resided in the closed city of Ozyorsk, even after they had ceased employment at Mayak. Furthermore, some information was available on factors such as smoking and alcohol consumption (Azizova et al., 2008).

(202) Having adjusted for non-radiation factors, there were significant increasing trends for both total external gamma dose and internal liver dose in the incidence of ischaemic heart disease among Mayak workers (Azizova et al., 2010a). The trend for internal dose was weaker and not significant after adjusting for external dose, whereas the external dose trend was little changed after adjusting for internal dose. The trend between external dose and mortality due to ischaemic heart disease was not significant, but was consistent with the corresponding incidence trend. There were also significant increasing trends in the incidence of, but not mortality from, cerebrovascular disease for both total external gamma dose and internal liver dose (Azizova et al., 2010b). Much of the evidence for raised morbidity from ischaemic

heart disease and cerebrovascular disease arose for workers with cumulative gamma doses of >1 Gy. Although the dose–response relationships for external radiation and circulatory disease incidence were consistent with linearity for ischaemic heart disease (ERR/Gy = 0.11, 95% CI 0.05–0.17) and cerebrovascular disease (ERR/Gy = 0.46, 95% CI 0.36–0.57), the statistical power to detect non-linearity at gamma doses of <1 Gy was low.

(203) A meta-analysis of epidemiological data on circulatory disease after low to medium radiation doses (average heart/brain doses all <2.5 Sv and mostly <0.5 Sv) suggested an aggregate ERR/Sv of 0.08 (95% CI 0.05–0.11) (Little et al., 2010). The aggregate ERR/Sv for stroke was 0.27 (95% CI 0.20–0.34), which was significantly higher than that for heart disease (ERR/Sv = 0.07, 95% CI 0.04–0.11). However, the ERR varied over at least two orders of magnitude in individual studies, indicating substantial heterogeneity, possibly as a result of confounding, which makes a causal interpretation of the results difficult (Little et al., 2010).

Astronauts and airline crew

(204) Astronauts are exposed to a mixture of radiations in space, including protons, heavy ions, and secondary neutrons, which differ in radiation quality and make individual dosimetry estimates difficult. Physical and biological doses for 19 astronauts at the International Space Station showed average effective doses for 6-month missions of 0.072 Sv (Cucinotta et al., 2008). There are currently no empirical data on radiation-related risk of cardiovascular disease among astronauts. An assessment of the risk is complicated by the large uncertainty in biological effectiveness of different space radiations, and the fact that astronauts are highly selected healthy individuals who have undergone rigorous health evaluations including cardiovascular examinations (Hamilton et al., 2006).

(205) Mortality from cardiovascular disease is markedly lower in airline crew compared with the general population, and tends to decrease with increasing duration of employment, consistent with a healthy worker–survivor bias, but providing no evidence of increased risk of cardiovascular disease among airline crew (Blettner et al., 2003; Zeeb et al., 2003).

Accidental exposures

(206) Fourteen years after the Chernobyl accident, the ERR/Gy for ischaemic heart disease was estimated to be 0.41 (95% CI 0.05–0.78) per Sv in the Russian cohort of 61,000 emergency workers with a mean dose of 0.109 Gy (Ivanov et al., 2006). However, the ERR/Gy was smaller (0.10), and not significantly elevated, in a subcohort of 29,000 emergency workers who were posted in the Chernobyl zone in the first year after the accident and who received a higher mean dose of 0.162 Gy. The ERR/Gy for cerebrovascular disease was significantly elevated in the entire cohort (0.45) and in the subcohort (0.39). Known confounding risk factors, such as excessive weight, hypercholesterolemia, smoking, and alcohol consumption, were not taken into account in these estimates.

2.5.3. Clinical data on therapeutic doses

Cardiac toxicity: randomised trials and epidemiological studies

(207) Radiation-induced heart disease in cancer survivors includes a wide spectrum of cardiac pathologies, such as coronary artery disease, myocardial dysfunction, valvular disorders, and pericardial disease. Electrical conduction abnormalities have also been reported but their association with radiation is less consistent (Stewart et al., 1995). Radiation-related heart diseases, except for pericarditis, usually present 10–15 years after exposure, although non-symptomatic abnormalities may develop much earlier. The long delay before symptomatic expression of damage probably explains why the radiation sensitivity of the heart has previously been underestimated.

(208) Cardiac effects have been investigated most extensively in long-term follow-up studies of patients with irradiated breast cancer and Hodgkin's lymphoma, although there are also data for other diseases, including childhood cancers. Epidemiological studies on survivors of Hodgkin's lymphoma show strongly elevated risks for cardiac deaths, with RRs in the range of 2–>7. This amounts to 15–40 extra cardiac deaths per 10,000 persons/year, depending on the age of the patients (increased risks for irradiation at young age), the radiation therapy methods used, and the follow-up time (Boivin et al., 1992; Hancock et al., 1993; Adams et al., 2003; Aleman et al., 2003; Swerdlow et al., 2007). Radiation causes both increased mortality (mainly fatal myocardial infarction) and increased morbidity. For instance, three- to five-fold increased standardised incidence ratios (SIR) of various heart diseases were observed in >1400 patients treated for Hodgkin's lymphoma before 41 years of age, relative to the general population, even after a follow-up of >20 years (Aleman et al., 2007). This study demonstrated that the risk was significantly greater for patients irradiated at a young age: the SIR for myocardial infarction was 2.6 (95% CI 1.6–4.0) for patients irradiated at 36–40 years of age compared with 5.4 (95% CI 2.4–10.3) for those irradiated at <20 years of age. The persistence of increased SIRs over prolonged follow-up time is of concern because this implies increasing absolute excess risks over time, due to the rising incidence of cardiovascular diseases with age. Prospective screening studies demonstrate that clinically significant cardiovascular abnormalities, such as reduced left ventricular dimensions, and valvular and conduction defects, are very common, even in asymptomatic Hodgkin's lymphoma survivors (Adams et al., 2004). Patients with Hodgkin's lymphoma also have a significantly higher risk (SIR 8.4, 95% CI 3.2–13.7) of requiring valve surgery or revascularisation procedures 15–20 years after radiotherapy (Hull et al., 2003).

(209) Two recent publications demonstrated significant increases in cardiovascular morbidity and mortality in long-term survivors of childhood cancers, including information on cardiac radiation doses (Mulrooney et al., 2009; Tukenova et al., 2010). Tukenova et al. (2010) reported on cardiovascular mortality in 4122 survivors of childhood cancer diagnosed before 1986 in France and the UK (median follow-up 26 years). The overall standardised mortality ratio was 8.3 compared with the corresponding general populations (95% CI 7.6–9.0). More than half of the cohort (2870)

received radiotherapy and the mean total dose to the heart was estimated for these patients. After accounting for sex, follow-up interval after diagnosis, age at diagnosis, and treatment period, the adjusted RR for cardiovascular death due to radiotherapy was 5.0 (95% CI 1.2–21.4). The RR of death from cardiovascular disease was significantly correlated with total mean heart dose [RR 12.5 (95% CI 1.4–116) and 25.1 (95% CI 3.0–209) for doses of 5–14.9 Gy and >15 Gy, respectively]. The ERR of cardiac mortality increased linearly with increasing dose (ERR at 1 Gy = 60%, 95% CI 20–250%), and the authors noted that this ERR level was not significantly higher than that reported for the atomic bomb survivors (17%/Sv, 95% CI 8–26%). However, for analyses restricted to fractionated doses of <5 Gy, there was no significant increased risk.

(210) The long-term cardiac outcomes of a large cohort (>14,000, mean follow-up 20 years) of survivors of childhood cancer, compared with sibling controls, are reported in a retrospective survey and analysis by Mulrooney et al. (2009). The cancer survivors had significantly increased reported incidences of congestive heart failure, myocardial infarction, pericardial disease, and valvular abnormalities compared with the siblings [hazard ratio (HR) 4.8–6.3]. In a multivariable analysis, cardiac irradiation with individual total fractionated doses of ≥ 15 Gy significantly increased the HR of congestive heart failure (15–35 Gy: 2.2, 95% CI 1.4–3.5; >35 Gy: 4.5, 95% CI 2.8–7.2), myocardial infarction (15–35 Gy: 2.4, 95% CI 1.2–4.9; >35 Gy: 3.6, 95% CI 1.9–6.9), pericardial disease (15–35 Gy: 2.2, 95% CI 1.3–3.9; >35 Gy: 4.8, 95% CI 2.8–8.3), and valvular abnormalities (15–35 Gy: 3.3, 95% CI 2.1–5.1; >35 Gy: 5.5, 95% CI 3.5–8.6) compared with non-irradiated cancer survivors. Lower doses were not associated with significantly increased risks, and the tendency towards an increased risk of pericardial disease after fractionated doses of 5–15 Gy was not significant (HR 1.9, 95% CI 0.9–3.9).

(211) Increased cardiac morbidity and mortality has been widely reported after treatment for breast cancer, especially using older radiotherapy techniques (Adams et al., 2003; Gaya and Ashford, 2005; Senkus-Konefka and Jassem, 2007). Although the RRs are lower than for patients with Hodgkin's lymphoma, the very large number of women irradiated for breast cancer makes this a significant health concern. The large number of randomised controlled trials carried out on patients with breast cancer also provides the opportunity to derive estimates of the causal effect of radiotherapy without bias from confounding factors or selection. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) evaluated the effects of local treatment on death from breast cancer and other causes in a collaborative meta-analysis of individual patient data from 23,500 women in 46 randomised trials of radiotherapy vs no radiotherapy with the same surgery, and from 9300 women in 17 trials of radiotherapy vs no radiotherapy with more extensive surgery (Clarke et al., 2005). This study showed a clear benefit of radiotherapy for local control and risk of death from breast cancer. However, there was, at least with some of the older radiotherapy regimens, a significant excess of non-breast cancer mortality in women randomised to receive radiotherapy [RR 1.12, standard error (SE) 0.04]. This excess risk was mainly from heart disease (RR 1.27, SE 0.07). A preliminary analysis of updated EBCTCG data (>30,000 women followed for up to 20 years after treatment) demonstrated that

the RR of cardiac death was related to the estimated cardiac dose, increasing by 31% per 10 Gy of mean total cardiac dose, without adjustment for fractionation effects (Darby et al., 2010). The risk for cardiac death was greater in irradiated women with left-sided (RR 1.44) vs right-sided (RR 1.18) breast cancer (estimated mean cardiac doses 12 and 5 Gy, respectively). This analysis also showed that the RR increased with time from irradiation (RR 1.08, SE 0.13 at 5 years compared with RR 1.63, SE 0.19 at >15 years). Until recently, the laterality of the tumour did not influence either the selection of women with breast cancer for radiotherapy or the technique used. Therefore, as the cardiac dose from radiotherapy is greater in women with left-sided breast cancer than in women with right-sided breast cancer, unbiased estimates of the effect of radiotherapy on heart disease can be derived from observational studies comparing rates of heart disease in populations of women with left-sided and right-sided breast cancer. Data from the Surveillance, Epidemiology and End-Results Cancer Registries (SEER) provide further convincing evidence of increased risk of myocardial infarction in women irradiated for breast cancer (Paszat et al., 1998; Darby et al., 2005). In a cohort of 308,861 women registered with breast cancer during the period 1973–2001, tumour laterality had no influence on subsequent mortality for women who did not receive radiotherapy. However, for irradiated women, there was a significant increase in cardiac mortality for left-sided vs right-sided disease (RR 1.2 overall and 1.4 at >10 years).

(212) A recent study has analysed the incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden followed for up to 30 years (McGale et al., 2011). Radiation-related risk was studied by comparing women with left-sided and right-sided tumours. Among unirradiated women, tumour laterality had little relevance to heart disease. Dose estimates were derived retrospectively for a representative sample of women in the study areas. The mean dose to the whole heart was 6.3 Gy for left-sided tumours and 2.7 Gy for right-sided tumours. The equivalent single doses would be approximately 4 Gy (left) and 2 Gy (right), allowing for dose fractionation effects. The fractionated doses produced significant left/right risk ratios for various heart disease endpoints (i.e. dose dependence). Mortality was similar in irradiated women with left-sided and right-sided tumours, but incidence ratios for left-sided vs right-sided tumours were raised: acute myocardial infarction 1.22 (95% CI 1.06–1.42), angina 1.25 (95% CI 1.05–1.49), pericarditis 1.61 (95% CI 1.06–2.43), and valvular heart disease 1.54 (95% CI 1.11–2.13). Incidence ratios for all heart disease were as high for women irradiated since 1990 (1.09, 95% CI 1.00–1.19) as for women irradiated between 1976 and 1989 (1.08, 95% CI 0.99–1.17), and were higher for women diagnosed with ischaemic heart disease prior to breast cancer than for other women [1.58 (95% CI 1.19–2.10) vs 1.08 (95% CI 1.01–1.15); *P* for difference = 0.01]. It was concluded that breast cancer radiotherapy has, at least until recently, increased the risk of developing ischaemic heart disease, pericarditis, and valvular disease. Women with ischaemic heart disease before a diagnosis of breast cancer may have incurred higher risks than others.

(213) Another study investigated treatment-specific incidence of cardiovascular diseases in >4000 10-year survivors of breast cancer treated from 1970 to 1986

(Hooning et al., 2007). When comparing patients with breast cancer who did or did not receive radiotherapy, radiation to the internal mammary chain was associated with significantly increased risk of cardiovascular disease (estimated mean fractionated dose to the heart 6–15 Gy), while for breast irradiation alone, no increased risk was observed (estimated mean fractionated dose to the heart <7 Gy). For patients treated before 1979, radiation was associated with HRs of 2.6 (95% CI 1.6–4.2) and 1.7 (95% CI 1.2–2.4) for myocardial infarction and congestive heart failure, respectively. For patients irradiated after 1979, the risk of myocardial infarction declined towards unity, but the risks for congestive heart failure and valvular dysfunction remained increased [HR 2.7 (95% CI 1.3–5.6) and 3.2 (95% CI 1.9–5.3), respectively].

(214) There are conflicting data concerning increased risks of radiation-associated cardiac disease in long-term survivors of testicular cancer. Some studies have shown increased risks of cardiovascular disease (Huddart et al., 2003) or cardiac death (Zagars et al., 2004) following infradiaphragmatic radiotherapy compared with surveillance alone. Other studies did not find a significant increase in the incidence of cardiovascular disease after subdiaphragmatic irradiation, although mediastinal irradiation was a risk factor (Van den Belt-Dusebout et al., 2006, 2007).

(215) Radiation-related cardiotoxicity in cancer patients can be influenced by additional treatment with systemic therapy. Combined modality treatment is increasingly used for cancer treatment, and several commonly used agents are known to be cardiotoxic (e.g. anthracyclines and trastuzumab). Whereas cardiotoxicity following radiotherapy is usually observed 5–10 years after treatment, anthracycline-related toxicity occurs at much shorter intervals. Anthracycline-related cardiotoxicity is caused by direct damage to the myoepithelium and it is strongly related to the cumulative drug dose (Steinherz, 1997; Kremer et al., 2001). A study of long-term survivors of Hodgkin's lymphoma showed that anthracycline-containing therapy further increased the risk of congestive heart failure and valvular disorders relative to radiotherapy alone [HR 2.8 (95% CI 1.1–5.5) and 2.1 (95% CI 1.3–3.5), respectively] (Aleman et al., 2007). The risks of myocardial infarction and angina were not further increased by anthracyclines. A study by Myrehaug et al. (2008) also suggested that the risk of clinically important cardiac toxicity following treatment for Hodgkin's lymphoma that includes both doxorubicin and mediastinal radiotherapy may be greater than that reported in prior studies of patients treated with radiotherapy alone. Anthracycline treatment was identified as an independent risk factor for cardiovascular mortality in long-term survivors of childhood cancer (Tukenova et al., 2010), but there was no significant interaction between radiation and chemotherapy in this study.

(216) The risk of cardiovascular diseases might also be increased through indirect effects of radiotherapy; for example, irradiation of the left kidney during para-aortic and spleen radiotherapy can lead to hypertension (Verheij et al., 1994). General risk factors for cardiovascular diseases such as hypertension, diabetes, hypercholesterolaemia, overweight, and smoking probably also contribute to the risk of cardiovascular diseases in patients treated with radiotherapy (Glanzmann et al., 1994; Bowers

et al., 2005; Harris et al., 2006; Hooning et al., 2007). It is not known whether the cardiovascular risk factor profile in patients treated for malignancies differs from that of the general population.

(217) Cardiovascular toxicity following radiotherapy and/or chemotherapy is expected to change in the future. On one hand, a decrease of toxicity is expected because of improved technical possibilities to reduce doses to the heart and major blood vessels. On the other hand, more combined modality treatment is used. Combination schedules containing cardiotoxic systemic therapy such as anthracyclines, taxanes, and newer medicines (e.g. trastuzumab) may influence the incidence of cardiovascular problems. In addition, intensity-modulated radiotherapy of lower-stage malignancies (e.g. dose-sculpting high-dose radiation therapy for lung cancer) may improve long-term survival and lead to a greater number of patients being at risk for radiation-induced heart disease. Due to the high incidence of lung cancer, this represents a large cohort of patients who previously died of their cancer but who may be at risk for development of radiation-induced cardiovascular disease in the future.

Dose and volume effects

(218) In a slow turnover tissue such as the heart, the risk of radiation injury is strongly influenced by dose per fraction or dose rate. Analysis of the clinical data for pericarditis after radiotherapy indicates a low α/β ratio of 2.5 Gy, which is consistent with estimates of 2–4 Gy from animal studies (McChesney et al., 1988; Gillette et al., 1989; Schultz-Hector, 1992). This indicates that large doses per fraction will be relatively more damaging to the heart than low doses per fraction (for the same total dose) and, indeed, increased complication rates were reported for patients with Hodgkin's lymphoma treated with 3×3.3 Gy/week compared with patients treated with 4×2.5 Gy/week for the same total dose (Cosset et al., 1988).

(219) When evaluating the relationship between exposure dose and risk of cardiac damage, account has to be taken of both the dose per fraction and the volume of heart exposed. In postoperative breast cancer, for example, the breast is generally treated with 50 Gy in 2-Gy fractions, and the tumour bed is frequently irradiated with at least 66 Gy in 2-Gy fractions. However, only a small part of the heart is exposed to high doses (depending on the treatment technique and tumour locality). Schultz-Hector and Trott (2007) estimated that, after correction for fractionation effects using the LQ model and an assumed α/β ratio of 1–3 Gy, equivalent single doses averaged over the entire heart are typically 1–2 Gy. They concluded that after such a correction for fractionation and volume effects, risk estimates for heart disease after radiotherapy for breast cancer are in the same range as those seen in the atomic bomb study (Preston et al., 2003) and peptic ulcer study (Carr et al., 2005). However, a more rigorous statistical evaluation of heterogeneity between epidemiological studies after low and moderate radiation exposures concluded that considerable heterogeneity between studies remained, even after correcting for fractionated dose delivery (Little et al., 2010). It therefore seems prudent to assess

dose–response relationships for cardiac damage separately for different exposed populations.

(220) The volume of the heart included in the irradiation field influences the risk of cardiotoxicity, although there are still many uncertainties regarding dose– and volume–effect relationships. A reduction in the increased risk of death from cardiovascular diseases other than myocardial infarction has been reported in patients with Hodgkin’s lymphoma treated after partial shielding of the heart and restriction of the total fractionated mediastinal dose to <30 Gy (Hancock et al., 1993). Radiotherapy techniques have greatly improved over the past 20 years, leading to more homogeneous dose distributions and reduced risk of toxicity (Lee et al., 1995). For pericarditis, TD 5/5 values (total dose for 5% incidence at 5 years) of 60 Gy, 45 Gy, and 40 Gy were estimated for one-third, two-thirds, and whole-heart irradiation using 2 Gy/fraction (Emami et al., 1991). However, lower mean heart doses of 26–27 Gy were subsequently found to be predictive of pericarditis in patients irradiated for oesophageal cancer (Martel et al., 1998; Wei et al., 2008). Heart volume exposed to 30 Gy (V_{30}) was also found to be predictive, with 13% and 73% pericarditis for V_{30} of <46% vs >46% (Wei et al., 2008).

(221) Dose–volume effects for long-term cardiac mortality have been analysed for patients with Hodgkin’s lymphoma and breast cancer (Gagliardi et al., 2001, 2010). These analyses show a smaller dependence of risk of damage on irradiated volume than for pericarditis. The predicted NTCP varied from approximately 7% to 20% for one-third to whole-heart exposure to 40 Gy (total fractionated dose). NTCP models further predicted that if <10% of the heart is exposed to 25 Gy (fractionated), the probability of cardiac mortality at 15 years is <1% (Gagliardi et al., 2010). There are also some indications of a volume effect from studies demonstrating that the extent of left ventricular radiation dose is an adverse prognostic factor of long-term radiation-induced heart disease (Levitt, 1992; Rutqvist et al., 1992; Girinsky et al., 2000; Marks et al., 2005).

(222) Several studies using functional imaging have shown myocardial perfusion changes at relatively short times after irradiation (<5 years) (Gyenes et al., 1996; Seddon et al., 2002; Marks et al., 2005). The largest of these studies showed that the incidence of perfusion defects was clearly related to the volume of the left ventricle included in the radiation field: 10–20% vs 50–60% reduction in perfusion for left ventricular volumes <5% and >5%, respectively (Marks et al., 2005). Although a relationship between these abnormalities and subsequent clinical heart disease may be expected, this has not been demonstrated to date.

(223) There is currently a major effort to use virtual simulation and CT planning techniques to estimate doses to various parts of the heart for breast cancer techniques used in the past (Taylor et al., 2007) and in the modern era (Nieder et al., 2007a), and to correlate this with risks for cardiotoxicity. It is already clear that modern CT-based planning of radiotherapy for breast cancer can reduce the mean heart volume receiving >50% of the tumour dose to <6% of the volume, compared with approximately 25% of the volume in older studies (Gaya and Ashford, 2005).

Radiation damage in major arteries

(224) Patients with head and neck cancer who receive high radiation doses of 60–70 Gy in 2-Gy fractions have significantly increased risk of carotid artery stenosis, reduced blood flow, and intima–media thickening (IMT), an early marker of atherosclerosis. One prospective study estimated that the rate of progression of IMT in irradiated patients with head and neck cancer was 21 times that expected in the general population (Muzaffar et al., 2000). Studies comparing left vs right IMT in carotid arteries of patients who received unilateral irradiation confirm that the increase in IMT is related to radiation dose rather than systemic factors in this high-risk patient population (Dorresteijn et al., 2005; Martin et al., 2005).

(225) Patients who have undergone neck dissection are at significantly greater risk of developing ipsilateral carotid artery stenosis after radiation therapy than patients who have not had neck dissection (Brown et al., 2005). The increased risk associated with neck dissection may be related to disruption of the vasa vasorum that invariably occurs when the vessels are ‘skeletonised’. In fact, radiation injury of the vasa vasorum may also be important in the pathogenesis of lesions of major arteries, including carotid artery stenosis (Murros and Toole, 1989; Zidar et al., 1997).

(226) Significantly increased risks of stroke have been described in adult patients treated with radiotherapy for head and neck cancer (60–70 Gy), with RRs in the range of 2–9, depending on follow-up and age at irradiation (Dorresteijn et al., 2002; Haynes et al., 2002; Scott et al., 2009). For example, Dorresteijn et al. (2002) showed that the RR of stroke was 3.7 (95% CI 1.3–8.0) for follow-up of <10 years, compared with 10.1 (95% CI 4.4–20.0) for follow-up of >10 years. The risk of stroke is also significantly elevated in long-term survivors of childhood leukaemia (RR 5.9, 95% CI 2.6–13.4) or brain tumours treated with >30 Gy of cranial radiotherapy (RR 38, 95% CI 17.6–79.9) (Bowers et al., 2006). The latter study demonstrated a relationship between radiation dose and RR of stroke, with significantly higher risks for cranial doses of >50 Gy compared with 30–50 Gy. Two large studies have identified an increased risk of stroke in patients with Hodgkin’s lymphoma treated with radiotherapy. A multi-institute cohort study examined the incidences of stroke in survivors of childhood Hodgkin’s lymphoma (median 40 Gy, mean age at treatment 13.8 years) (Bowers et al., 2005). The incidence of self-reported stroke was significantly increased compared with sibling controls (RR 4.3, 95% CI 2.0–9.3). A slightly lower risk of clinically verified stroke (SIR 2.2, 95% CI 1.7–2.8) and transient ischaemic attack (SIR 3.1, 95% CI 2.2–4.4) was reported in a recent analysis of older patients irradiated for Hodgkin’s lymphoma (De Bruin et al., 2009). In this study, only 25% of the patient population were <20 years of age at the time of treatment; this younger group was at greater risk of cerebrovascular damage than the total cohort (stroke: SIR 3.8, 95% CI 1.6–7.4; transient ischaemic attack: SIR 7.6, 95% CI 2.4–17). A systematic review including 6908 patients from institutional series or cohort analyses comparing the frequency of cerebrovascular events in irradiated vs non-irradiated patients showed a significantly increased risk of 9.0 (95% CI 4.9–16.7) after neck and supraclavicular radiotherapy (Scott et al., 2009).

(227) There is much less agreement on whether radiation is a significant risk factor for stroke in patients with breast cancer. One observational study reported a non-significant increased risk of cerebrovascular attack among 820 early breast cancer patients treated with modern radiotherapy techniques (Jagsi et al., 2006). A much larger, population-based study of >25,000 women with breast cancer showed a small, but significant, increase in the incidence of cerebral infarction (RR 1.1, 95% CI 1.07–1.17), but no increased risk for cerebral haemorrhage compared with the general population (Nilsson et al., 2005). However, no information on individual treatment schedules or cardiovascular risk factors was available, which makes it difficult to evaluate the role of irradiation. In a nested case–control study of stroke after treatment for breast cancer (Nilsson et al., 2009), radiotherapy to internal mammary chain and supraclavicular nodes showed a non-significant increase in stroke [odds ratio (OR) 1.3, 95% CI 0.8–2.2] compared with no radiotherapy, although a pooled analysis of radiotherapy to internal mammary chain and supraclavicular nodes compared with no radiotherapy or radiotherapy excluding internal mammary chain and supraclavicular nodes showed a significant increase (OR 1.8, 95% CI 1.1–2.8). In contrast, another large cohort study (>4000 10-year survivors of breast cancer) which specifically investigated the risk of ischaemic stroke in relation to breast cancer treatment also showed no increased risk associated with radiotherapy, although there was an increased risk associated with hormonal therapy (Hoening et al., 2006). The EBCTCG collaborative meta-analysis of patient data from 46 randomised trials also showed that the risk of stroke was not significantly increased by radiotherapy (Clarke et al., 2005). It is possible that the reported increases in stroke in some of the observational studies may be due to selection bias or confounding factors.

Intracoronary brachytherapy

(228) The treatment of coronary artery disease has changed over the last decades from medical treatment, to percutaneous transluminal coronary angioplasty, to implantation of coronary stents, to implantation of drug-eluting stents and intracoronary brachytherapy (Dawkins et al., 2005). The rationale for using ionising radiation to prevent restenosis emerged from the understanding that neointimal hyperplasia represented a proliferative response to percutaneous transluminal coronary angioplasty and stenting (Sindermann et al., 2004). Radiation potentially offers an effective means of dealing with that response. Trials of intraluminal irradiation, either using a radioisotopic stent or intraluminal brachytherapy, revealed impressive results, with up to four-fold decreases in restenosis reported after delivering a single 10-Gy dose to the vessel wall. Several studies demonstrate some benefit from gamma and beta emitters for the treatment of in-stent restenosis, but this is not a universal finding.

(229) The situation was different for the treatment of newly diagnosed stenosis with radioactive stents or intraluminal brachytherapy. Those studies revealed either aneurysmatic alterations of vessels, edge effects (restenosis at the ends of the stent), or simply failed to show any prevention of restenosis. Edge restenosis is considered to be the result of the fall-off in the radiation dose at the edges of the stent. It was

proposed that this may exert a proliferative stimulus (as observed using cell cultures) on the smooth muscle cells of the vessel wall, resulting in a neointima at the site of the stent edges after these lower doses of irradiation. Late arterial thrombosis and vessel occlusion has also been demonstrated after coronary brachytherapy. Animal studies demonstrated reduced endothelial cell function and incomplete re-endothelialisation at 6 months. This, along with persistent fibrin deposition and continuous platelet recruitment, probably contributes to the risk of late thrombosis (Farb et al., 2003).

(230) Radiation protection problems and the edge effects associated with radioactive stents lead to the development of drug-eluting stents, which are now in common use. There has been a consistent finding of impaired neointima formation in both animal models and patients for a variety of arteries, such as femoral and coronary arteries. A meta-analysis of randomised trials assessing the outcome of vascular brachytherapy or drug-eluting stents for the treatment of coronary artery restenosis showed that vascular brachytherapy improved the long-term outcome of angioplasty compared with bare metal stents alone. Drug-eluting stents appeared to provide similar results to vascular brachytherapy during short-term follow-up (Oliver et al., 2007). Although short-term follow-up data seem promising, intracoronary brachytherapy is not widely used (Thomas, 2005). In addition, long-term follow-up data after intracoronary brachytherapy and drug-eluting stents are still lacking.

2.5.4. Experimental data and mechanisms of damage

(231) Damage to the vascular endothelium of large arteries increases the risk of atherosclerosis, vascular stenosis, and thromboembolism (Stewart et al., 1995; Veinot and Edwards, 1996; Adams and Lipshultz, 2005). Early inflammatory changes in the endothelial cells of irradiated large vessels lead to monocyte adhesion and transmigration into the subendothelial space. In the presence of elevated cholesterol levels, these invading monocytes transform into activated macrophages that ingest lipids and form fatty streaks in the intima, thereby initiating the process of atherosclerosis. Major arteries such as coronary and carotid arteries are the most susceptible to atherosclerotic plaque formation, especially at bifurcations (branching sites). Proliferation of myofibroblasts is also stimulated by the production of inflammatory cytokines, resulting in further reduction of the arterial lumen.

(232) Experimental animal studies have shown that radiation doses of ≥ 2 Gy are associated with increased expression of various inflammatory cytokines and adhesion molecules in endothelial cells of both the microvasculature and large vessels (Schultz-Hector and Trott, 2007; Little et al., 2008). When combined with elevated cholesterol levels, this accelerates the development of atherosclerosis, leading to increased size and number of atherosclerotic lesions, and predisposes to the formation of macrophage-rich, unstable plaque, rather than stable collagenous plaque (Vos et al., 1983; Tribble et al., 1999; Pakala et al., 2003; Stewart et al., 2006). Such lesions are more likely to rupture and cause a fatal heart attack or stroke.

(233) In contrast, whole-body doses of 0.1–0.6 Gy have been shown to inhibit leukocyte adhesion to endothelial cells in rats (Arenas et al., 2006), and doses of 0.025–0.05 Gy exerted some protective effects on the development of atherosclerosis in ApoE^{-/-} mice, particularly at low dose rates (Mitchel et al., 2011). This suggests a non-linear dose–response relationship for radiation-induced atherosclerosis, which may be relevant to some epidemiological observations of a protective cardiovascular effect from very-low-dose occupational exposures (0.02 Sv), but detrimental effects at higher doses (0.2 Sv) (Vrijheid et al., 2007a).

(234) In the heart, radiation-induced damage to the myocardium is primarily caused by damage to the microvasculature, leading to inflammatory and thrombotic changes, capillary loss, focal ischaemia, and interstitial fibrosis after high doses (Adams et al., 2003; Schultz-Hector and Trott, 2007). Radiation-related valvular disease cannot be explained by microvascular damage since valves do not have blood vessels. However, it is possible that this damage is consequential to late damage of the surrounding myocardial endothelium leading to fibrosis. It is not clear whether conduction abnormalities and arrhythmias, which are frequently observed after irradiation (Adams et al., 2004), are related to autonomic dysfunction or compensate for decreased cardiac output.

(235) After high doses to the heart (>40-Gy fractionated dose), acute pericarditis (protein-rich exudate in the pericardial sac) is likely to develop within 6 months. This may resolve in time but can also progress to fibrin deposition, leading to a thickened pericardial sac and chronic constrictive pericarditis.

(236) After lower doses, the earliest morphological changes seen in the irradiated heart are changes in the function of capillary endothelial cells, leading to lymphocyte adhesion and extravasation. This is followed by thrombi formation, obstruction of the microvessels, and decreases in capillary density, accompanied by loss of the endothelial cell marker alkaline phosphatase (Fajardo and Stewart, 1970; Lauk, 1987; Schultz-Hector, 1992; Fajardo et al., 2001). Although the remaining capillary endothelial cells respond to damage with increased proliferation (Lauk and Trott, 1990), this is inadequate to maintain proper microvascular function. Progressive reduction in the number of patent capillaries eventually leads to ischaemia, myocardial cell death, and fibrosis.

(237) Myocardial degeneration, seen from approximately 10 weeks after irradiation, coincides with the first signs of decreased cardiac function in rats. However, further decreases in function do not occur until shortly before the onset of fatal congestive heart failure, despite increasing degeneration of myocardial mass (Schultz-Hector, 1992). In contrast, both stroke volume and myocardial contractility deteriorated much more rapidly in the enervated heart *ex vivo* (Franken et al., 1997). This is probably explained by compensatory mechanisms operating *in vivo* and masking the extent of functional damage.

(238) Experimental studies indicate that radiation injury to the capillary network is an important contributor to myocardial degeneration and heart failure after irradiation (Schultz-Hector and Trott, 2007). This is supported by clinical studies that demonstrate regional perfusion defects in non-symptomatic breast cancer patients 6 months–5 years after radiotherapy (Gyenes et al., 1996; Seddon et al., 2002; Marks

et al., 2005). Experimental studies in rabbits, rats, and dogs have also shown that high single doses of 16–20 Gy to the heart induce an exudative pericarditis within 70–100 days (Fajardo and Stewart, 1970; Gavin and Gillette, 1982; Lauk et al., 1985; McChesney et al., 1988). This is associated with oedema, fibrotic thickening, and adhesions of the epicardium and pericardium, and is probably due to damage and cell death of the mesothelial cells.

(239) Microvascular changes and accelerated atherosclerosis, described above, are the likely underlying causes of radiation-induced cardiovascular damage after medium to high doses to part of the heart or the whole organ, such as after radiotherapy to the thorax. However, it seems likely that other mechanisms are responsible for cardiovascular effects after whole-body exposures at much lower doses. Persistent increases in pro-inflammatory cytokines and long-term impairment of T-cell-mediated immunity, as seen in atomic bomb survivors (Kusunoki et al., 1999; Hayashi et al., 2003) may well be involved. It has also been postulated that radiation-induced genomic instability (Schultz-Hector and Trott, 2007), or monocyte killing and increased levels of monocyte chemo-attractant protein 1 (Little et al., 2010) may play a role in initiation and progression of atherosclerosis after low doses.

2.5.5. Summary

(240) Data from the Life Span Study cohort of Japanese atomic bomb survivors show an excess risk of mortality from circulatory disease. The ERR/Gy based on the linear model is estimated to be 0.14 (95% CI 0.06–0.23) for heart disease overall (ICD9 codes: 390–398, 402, 404, 410–429) and 0.09 (95% CI 0.01–0.17) for cerebrovascular disease (ICD9 codes: 430–438) for 1950–2003. The shape of the dose–response curve is consistent with linear, LQ, and quadratic relationships, although the data for heart disease tend to favour a linear relationship. For heart disease, the best estimate of the dose–effect threshold is 0 Gy (i.e. no threshold; 95% CI <0–0.5 Gy), whereas it is 0.5 Gy for cerebrovascular disease.

(241) Excess risks of circulatory disease have also been reported from some, but not all, populations with accidental or occupational total-body exposures, but there is substantial heterogeneity in the association between radiation exposure and circulatory disease, due, at least in part, to confounding effects. There is considerable uncertainty about the shape of the dose–response curve at doses of <0.5 Gy.

(242) There are excess risks of heart disease for patients given radiotherapy with estimated average heart doses of 1–2 Gy (single dose equivalent, after correction for dose fractionation effects). Excess risks of cardiovascular disease only become apparent 10–20 years after exposure at low doses. Long follow-up times are therefore required for assessment of risk.

(243) Radiation-induced heart disease can occur as a result of both microvascular damage to the myocardium, leading to focal myocardial degeneration and fibrosis, and accelerated atherosclerosis in major blood vessels.

2.6. Eye

2.6.1. Anatomical features and proliferative organisation

(244) The lens is an optically clear, avascular tissue that receives nourishment from its surrounding aqueous and vitreous fluids (Harding and Crabbe, 1984). Its anatomy is unique, with a single epithelial cell layer on the anterior, corneal-facing surface that contains the progenitors of the underlying lens fibre cells (Horwitz and Jaffe, 1992). The lens is completely encased by a basement membrane, termed the 'lens capsule'. Lens transparency depends on the proper differentiation of lens fibre cells from a proliferating subset of a single layer of epithelial cells on the lens anterior surface. Throughout life, epithelial cells located at the periphery of the lens, in the germinative zone, divide and differentiate into mature lens fibre cells. These terminally differentiated cells do not contain nuclei or mitochondria, and are dependent on the overlying epithelial cell layer for nutrient transport, energy production, and protection from insulting agents. While this process slows considerably during puberty, the lens continues to grow throughout life, eventually tripling in weight (Kleiman and Worgul, 1994). Due to the unique anatomy of the lens, disruption of the integrity of the epithelial cell layer is likely to lead to cataract (Cogan et al., 1952; Von Sallmann, 1957; Worgul et al., 1989).

(245) From early in embryogenesis, lens growth is entirely determined by proliferation of a small band, approximately 60 cells wide, in an area of the anterior epithelium near the lens equator termed the 'germinative zone'. The mitotic index of cells more anterior to this region, in the central zone, is negligible (Von Sallmann et al., 1962; McAvoy, 1978), but these cells in the central zone play an important role in maintaining lens metabolism and homeostasis (Kuck, 1970). Following terminal cell division, cells in the germinative zone migrate towards the equator and queue up in precise registers called 'meridional rows'. There, they begin to differentiate into mature lens fibre cells. Since mitosis is only 1 h in duration, and given that the human lens epithelial population remains constant after the age of 2 weeks (Von Sallmann, 1957), one layer of new fibre cells is created approximately every 8 h. Qualitatively, the same phenomena are true for all mammalian lenses. As ageing proceeds, the rate of fibre cell formation decreases but never stops (Harding et al., 1971).

2.6.2. Cataract formation

Background

(246) The principal pathology of the lens is its opacification, termed 'cataract' in its advanced stages (Van Heyningen, 1975). There are three predominant forms of cataract depending on their anatomical location in the lens: cortical, involving the outer, more recently formed lens fibre cells; nuclear, developing first in the inner embryological and fetal lens fibre cells; and posterior subcapsular (PSC), developing from the dysplasia of transitional zone epithelial cells and resulting in an opacity at the posterior pole (Kuszak and Brown, 1994).

(247) Cataract is the leading cause of blindness worldwide, especially in less-affluent countries where surgical treatment is often unavailable (WHO Programme Advisory Group, 1989; Thylefors, 1999; Shichi, 2004). More than 25 million blind and 119 million visually impaired individuals are affected (Thylefors et al., 1995; Arnold, 1998; Thylefors, 1999; WHO, 2004). Evidence of lens opacities can be found in >96% of the population aged >60 years (Luntz, 1992). The only treatment for cataract is surgical removal; a procedure that consumes 12% of the Medicare budget overall, and 60% of all Medicare costs related to vision in the USA (Stark et al., 1989; Ellwein and Urato, 2002). Given the increasing human life span, the societal burden of cataract surgery is expected to worsen in future years (Kupfer, 1985; WHO, 1997; Congdon et al., 2004; EDPR Group, 2004).

(248) The lens of the eye is one of the most radiosensitive tissues in the body (Brown, 1997; Ainsbury et al., 2009). When the radiosensitivity of various eye tissues is compared, detectable lens changes are noted at doses between 0.2 and 0.5 Gy, whereas other ocular pathologies in other tissues occur after acute or fractionated exposures of between 5 and 20 Gy.

(249) Ocular radiation exposure results in characteristic lens changes including cataract (Cogan and Donaldson, 1951; ICRP, 1969; Merriam and Worgul, 1983; NCRP, 2000; Kleiman, 2007). Initial stages of lens opacification do not usually result in visual disability, but the severity of these changes may progressively increase with dose and time until vision is impaired and cataract surgery is required (Merriam et al., 1983; Lett et al., 1991; NCRP, 2000; Neriishi et al., 2007). The latency of such changes is inversely related to dose.

(250) In spite of the well-documented history of radiation-induced cataract (Bellows, 1944; Ham, 1953; Lerman, 1962; Radnot, 1969; Bateman, 1971; Merriam et al., 1972; Worgul and Rothstein, 1977; Koch and Hockwin, 1980), there is still considerable uncertainty surrounding the relationship between dose and radiation cataract development, which is of concern to the risk assessment community. Present ocular guidelines are predicated on the view that cataractogenesis is a deterministic event and requires a threshold radiation dose before lens opacities will develop (ICRP, 1991a,b; NCRP, 2000). ICRP has published threshold values for detectable opacities of 5 Sv for chronic exposures and 0.5–2.0 Sv for acute exposures (ICRP, 2007). ICRP and NCRP have reported threshold values for visually disabling cataracts of 2–10 Sv for single brief exposures and >8 Sv for protracted exposures (NCRP, 1989; ICRP, 2007). Nevertheless, in its latest recommendations, ICRP (2007) stated that ‘recent studies have suggested that the lens of the eye may be more radiosensitive than previously considered. However, new data on the radiosensitivity of the eye with regard to visual impairment are expected.’

(251) In recent years, a number of new studies have suggested an elevated risk for cataract development in populations exposed to low doses of ionising radiation below these assumed thresholds. For example, dose-related lens opacification has been reported at exposures significantly lower than 2 Gy among those undergoing CT scans (Klein et al., 1993) or radiotherapy (Wilde and Sjostrand, 1997; Hall et al., 1999), astronauts (Cucinotta et al., 2001; Rastegar et al., 2002;

Chylack et al., 2009), atomic bomb survivors (Nakashima et al., 2006; Neriishi et al., 2007), residents of contaminated buildings (Chen et al., 2001b; Hsieh et al., 2010), victims of the Chernobyl nuclear accident (Day et al., 1995; Worgul et al., 2007), radiological technologists (Chodick et al., 2008), interventional radiologists (Junk et al., 2004), and interventional cardiologists (Kleiman et al., 2009; Vañó et al., 2010). These human epidemiological studies, as well as recent work with experimental radiation cataracts in animals, suggest that cataracts may occur following exposure to significantly lower doses of ionising radiation than assumed previously. Such observations have implications for individuals undergoing radiotherapy or diagnostic procedures, and for those occupationally exposed to ionising radiation, such as interventional medical personnel, nuclear workers, and astronauts.

(252) Not all recent studies, however, support the observation of a lower threshold for radiation cataracts. The Blue Mountains Eye Study (Hourihan et al., 1999) failed to find an association between radiation exposure in individuals undergoing CT scans and cataract prevalence, although these doses were probably <0.10 Gy, and a threshold between 0.10 and 0.50 Gy cannot be excluded. Similarly, Chmelevsky et al. (1988) rejected the concept of a zero threshold for lens opacification in patients treated with ^{224}Ra . Guskova (1999), in reviewing Russian nuclear industry data, indicated that chronic exposure to ionising radiation with a cumulative exposure of <2 Gy was not associated with cataract development.

(253) The concept of a dose threshold is critical not only to risk assessment but also to theories regarding the pathological mechanisms of radiation cataracts. It should be noted that early studies of radiation cataracts generally had short follow-up periods, failed to consider the increasing latency period as dose decreases, did not have sufficient sensitivity to detect early lens changes, and had relatively few subjects with doses below a few Gy (Leinfelder and Kerr, 1936; Cogan and Dreisler, 1953; Cogan et al., 1952; Merriam and Focht, 1962). It should also be noted that there is considerable heterogeneity in the approaches used to document radiation-associated lens opacities. Radiation cataracts have been observed using retro-illumination, ophthalmoscopy, conventional slit-lamp examination, and Scheimpflug imaging. Epidemiological studies have used self-reporting, medically documented lens opacities, or the frequency of cataract extraction surgery. Scoring systems for lens opacities have also varied, including use of Lens Opacity Classification System (LOCS) II, LOCS III, Merriam–Focht, modified Merriam–Focht, focal lens defects (FLD), and a variety of other approaches. It is also recognised that there is variability among clinicians and investigators in the precise clinical definition of a radiation cataract, and a diversity of opinion as to whether all detectable lens changes, given sufficient time, will progress to visually disabling cataracts. Lastly, it should be recognised that the purpose of radiation protection is to prevent tissue-damaging effects of clinical significance, and to limit effects to levels that are acceptable, modulated by societal concerns. Current exposure guidelines are based on terrestrial radiation exposure. Since radiation exposures in space are relatively difficult to reduce and impossible to

eliminate entirely, larger annual doses are permitted for astronauts than are recommended for radiation workers on the ground, although career limits of risk are approximately equal (NCRP, 1989, 1993, 2000).

Examination and quantitation of lens changes

(254) The earliest radiation-induced lens change is the visualisation of an opalescent sheen on the posterior lens capsule observed by slit-lamp examination (Worgul et al., 2007). This is followed by the appearance of small vacuoles and diffuse punctate opacities centred around the posterior lens suture.

(255) One prominent scoring method, the Merriam–Focht technique (Merriam and Focht, 1962), has been used extensively, with slight modification, for decades (Merriam and Worgul, 1983; Worgul, 1986; Brenner et al., 1996; Kleiman, 2007; Worgul et al., 2007; Vañó et al., 2010). The method relies upon the fact that radiation cataracts develop in a characteristic sequential and progressive fashion. Merriam–Focht scoring was specifically designed to detect very early lens changes due to ionising radiation exposure. At least four readily distinguishable stages are identifiable by slit-lamp biomicroscopy. These form the basis for a quantitative classification system to gauge cataract severity. For example, if fewer than 10 dots or five vacuoles are noted, a Stage 0.5 cataract is scored. If more than these are noted but the anterior region is transparent, a Stage 1.0 cataract is scored. Continued cataract development leads to progression of these posterior changes, including involvement of the anterior subcapsular region and, eventually, visual disability. It should be noted that Stages 2 and higher are those generally associated with visual disability. Lower stages of opacification are not usually perceived by the subject as a change in vision. Cataract scoring continues until total opacification of the lens is documented. This approach was used in the study of Chernobyl ‘liquidators’ (Worgul et al., 2007).

(256) Another system, FLD, uses retro and transverse illumination of the lens and additive scoring of minor dot-like opacities, flakes, and vacuoles in the posterior, nuclear, and cortical regions of the lens (Day et al., 1995; Chen et al., 2001b).

(257) Yet another system uses digitised Scheimpflug slit images of the lens nucleus region and retro-illumination images of the cortical and PSC regions to generate a value representing the relative area of each region that is opaque (Chylack et al., 2009).

(258) A commonly used approach for quantitating cataracts of various aetiologies is based on LOCS II (Chylack et al., 1989) or III (Chylack et al., 1993). LOCS III provides a simple and accurate means to subjectively grade cataract type and severity by comparing an individual’s lens image with a set of standard photographs that illustrate differing severity of nuclear, cortical, and PSC cataracts. This approach has been used in atomic bomb screening studies (Minamoto et al., 2004; Nakashima et al., 2006). It should be noted, however, that LOCS III methodology does not include a scoring system for the early posterior lens changes, such as flecks, dots, and vacuoles, which are typically associated with nascent ionising-radiation-associated lens damage.

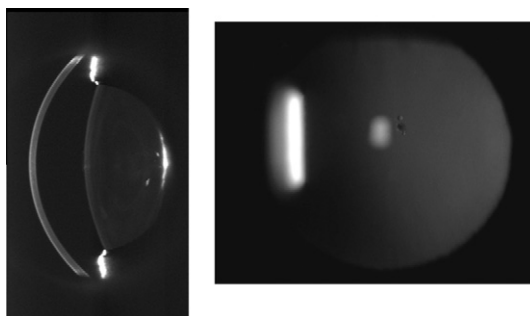


Fig. 2.7. Left: Typical Scheimpflug slit lamp biomicroscopic image of a human posterior subcapsular radiation cataract. Right: Retro-illumination image of an early posterior lens change associated with radiation exposure.

(259) A typical Scheimpflug image of a human radiation cataract is shown in Fig. 2.7 (left), and a typical retro-illumination image of minor posterior lens changes, including dots and vacuoles, is shown in Fig. 2.7 (right).

(260) The clinicohistopathological changes accompanying radiation cataractogenesis are characteristic and similar in all vertebrate lenses. Initial presentation usually involves a lens opacity originating along the visual axis, often in the PSC region of the lens. The prevalence of cataracts in humans is generally low below 60 years of age, and PSC cataracts only represent a small fraction of cataract types at any age (EDPR Group, 2004; Varma and Torres, 2004; Klein et al., 2008). Only a modestly increased age-related risk for PSC cataracts has been reported (Varma and Torres, 2004). While other environmental insults may also result in PSC cataract formation, such as corticosteroid treatment (Urban and Cotlier, 2006), chronic uveitis (Worgul and Merriam, 1981), diabetes (Jeganathan et al., 2008), or galactosaemia (Beigi et al., 1993), radiation exposure is generally associated with this type of lens opacification (Cogan et al., 1952; Worgul et al., 1976; Merriam and Worgul, 1983). Cataracts from sunlight or ultraviolet (UV) light, or infrared exposure, are generally associated with superficial cortical opacification (Robman and Taylor, 2005; see Paras 257 and 258). Similarly, smoking, which is a risk factor for some types of lens opacities, is most strongly associated with nuclear cataract (West et al., 1989; Hiller et al., 1997; Robman and Taylor, 2005). It should be noted, however, that anterior subcapsular and cortical changes have also been associated with ionising radiation exposure (Hall et al., 1999; Minamoto et al., 2004; Nakashima et al., 2006; Chylack et al., 2009; Blakely et al., 2010).

(261) The rate at which these changes develop, regardless of anatomical location, is strongly dose-dependent with an age-modulating component (Merriam and Focht, 1962; Merriam et al., 1972; Merriam and Szechter, 1973, 1975). The lens epithelium appears to be most sensitive to ionising radiation during the period of rapid lens growth in infancy. Once past adolescence, experimental animal work suggests that for doses of <3 Gy, the rate of progression is greater in older individuals, and a correspondingly faster time of onset is noted (Merriam and Szechter, 1975). Radiation

cataracts are inversely related to dose and depend on the rate at which damaged lens epithelial cells divide, aberrantly differentiate, and migrate to the posterior pole (Worgul and Rothstein, 1975).

(262) Regarding cataracts from infrared radiation, historically these have been noted in glassblowers and furnace workers. It is considered that thermal mechanisms are involved, and/or heat transfer from the iris or cornea (Okuno, 1994; Vos and Norren, 2004). In humans, initial and acute presentations usually include a characteristic exfoliation-like pathology of the zonular region in the anterior capsule which is considered to be pathognomonic (Karp et al., 1991; Brown and Bron, 1996). Although some have suggested that PSC cataracts and other types of lens opacities may develop much later following exposure, such evidence is equivocal, and anterior capsular and peripheral cortical changes appear to precede posterior lens changes. In an experimental rabbit model, acute exposure was associated primarily with anterior subcapsular changes (Pitts and Cullen, 1991). Vogt (1932), Goldmann (1933), and Langley et al. (1960) described initial changes in the anterior cortical regions of the lens with posterior lens involvement, if at all, only occurring at later stages of opacification. This temporal sequence of lens changes is not found in ionising-radiation-induced cataract. The thermal basis for infrared cataract formation suggests a role for protein denaturation and misfolding in its aetiology; features not normally associated with ionising radiation exposure of the lens and consequent aberrant lens epithelial cell differentiation. Any confounding influence of infrared exposure on ionising-radiation-induced cataracts seems unclear.

(263) Concerning UV exposures, epidemiological evidence suggests an association between elevated UVB exposure and the risk of cortical cataracts (Taylor et al., 1988). The inferonasal quadrant of the lens appears to be at greatest risk (Schein et al., 1994), likely due to optical properties of the eye and reflection of sunlight and UV light from the nose and skin predominantly on to this region of the lens (Coroneo et al., 1991). The influence of UV exposure on ionising-radiation-induced cataracts has been studied in the atomic bomb survivors (see Para. 267).

Dose response and cataract threshold

(264) The ocular-radiation protection standards, formulated by NCRP and ICRP, are all predicated on the assumption that radiation cataracts are deterministic and only appear when a threshold dose is exceeded. For detectable opacities, this value is currently 0.5–2 Gy for acute exposures and 5 Gy for chronic exposures (ICRP, 2007). For visually disabling cataracts, the values are higher, with a dose threshold of between 2 and 10 Gy for acute exposures and 8 Gy for chronic exposures. Several recent lines of evidence from experimental and epidemiological studies have, however, suggested that these values may be too high, and that radiation cataracts may be stochastic. In part, this re-evaluation of the data is based on the presumption that detectable opacities, given enough time, will progress to visual disability.

(265) This is an important distinction since, if there is zero threshold for radiation cataracts, current radiation safety standards for workers as well as the general population may be inadequate. It is therefore essential for the risk-assessment

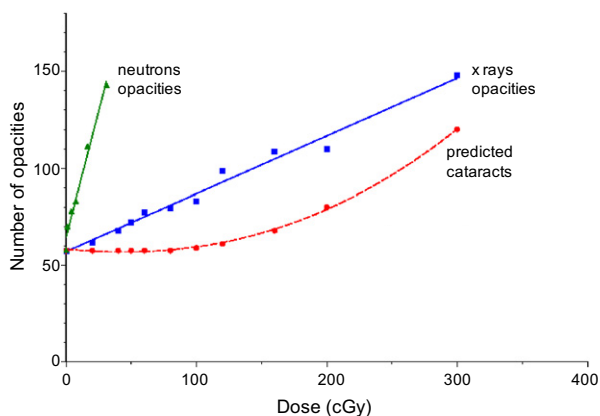


Fig. 2.8. Number of opacities in the murine lens as a function of 250-kVp x rays or 14-MeV neutrons, taken from Di Paola et al. (1978). The dashed line (added by the present authors) represents the shape of a curve for x rays that would be predicted for cataracts, if a cataract results from the accumulated damage to many lens cells i.e. the fusing of multiple opacities.

community to know whether visually disabling cataract formation is a stochastic response to radiation; a question that may be resolved in the future by a combination of human epidemiological approaches and animal studies.

(266) At a microscopic level, radiation damage to single lens epithelial or fibre cells probably results in small localised changes in lens transparency, and is therefore a stochastic event. Support for this hypothesis is provided by the linear relationship between radiation dose and the number of small, discrete dots in the posterior lens cortex of animals exposed to either low- or high-LET radiation (Di Paola et al., 1972) (Fig. 2.8). Di Paola et al. suggested that accumulation and coalescence of these micro-opacities results in populations of damaged lens fibre cells that form larger lens defects, eventually resulting in a clinical opacity. Chylack et al., in the NASA Study of Cataract in Astronauts, used a similar approach to score PSC ‘centres’, and suggested a relationship between galactice cosmic radiation exposure and the size of the PSC cataract (Chylack et al., 2009; Blakely et al., 2010). Using this approach, if a minimum number of damaged cells was required before lens opacity was clinically observed, this would suggest a requirement for a threshold radiation dose, and therefore radiation cataracts could be classified as a ‘deterministic’-type response (see dashed line in Fig. 2.8). Note also that although the frequency of lesions is a function of dose, there is no direct evidence that the quality of the lesions is dose-dependent.

(267) On the other hand, radiation cataract formation could be explained by initial damage to a single lens epithelial cell which, upon cell division and differentiation, results in groups of defective lens fibre cells, all of which are progeny of a single damaged progenitor lens epithelial cell. Support for this hypothesis is provided by animal experiments which demonstrated that radiation cataracts will not form if epithelial cell division is inhibited (Worgul and Rothstein, 1975, 1977; Rothstein et al.,

1982; Holsclaw et al., 1989, 1994) or if the dividing portion of the lens epithelium is shielded from exposure (Alter and Leinfelder, 1953; Puntenney and Schoch, 1953; Leinfelder and Riley, 1956; Pirie and Flanders, 1957). In this case, radiation cataract development would be stochastic. Under this scenario, a-priori DNA damage to a subset of the lens epithelial cells is required before radiation cataracts can form. Support for the stochastic theory of radiation cataract development is provided by a number of human epidemiological studies, detailed below, as well as animal model systems, described in section 2.6.4.

2.6.3. Epidemiological studies

(268) The accessibility of the lens to repeated, non-invasive measurement facilitates long-term studies of low-dose radiation exposures. Epidemiological studies of cataract onset or progression in human populations exposed to low doses of radiation should help to reduce the uncertainty surrounding the concept of a dose threshold for radiation cataracts. Such studies may help to determine whether current dose limits are appropriate and/or provide insights into the relevance of radiation cataracts to overall human health and radiosensitivity (Table 2.4).

(269) A previous review of epidemiological literature indicated that some findings are consistent with the absence of a dose threshold (Shore and Worgul, 1999). One of the critical questions surrounding the concept of a dose threshold for cataractogenesis is whether documentation of low-dose radiation-related changes in the transparency of the lens is sufficient for purposes of setting regulatory standards and risk estimates for cataractogenesis. This approach assumes that, given sufficient time, such lens changes will progress to eventual loss of visual acuity or changes in contrast sensitivity requiring surgical removal of the cloudy lens. This issue remains

Table 2.4. Human epidemiological studies that support or question a lower or zero threshold model for radiation cataracts.

<i>Studies supporting a lower or zero threshold</i>	
Diagnostic procedures	Klein et al. (1993)
Radiotherapy	Albert et al. (1968), Wilde and Sjostrand (1997), Hall et al. (1999)
Astronaut core	Cucinotta et al. (2001), Rastegar et al. (2002), Chylack et al. (2009)
Atomic bomb survivors	Minamoto et al. (2004), Nakashima et al. (2006), Neriishi et al. (2007)
Residents of contaminated buildings	Chen et al. (2001b), Hsieh et al. (2010)
Nuclear plant workers	Jacobson (2005)
Chernobyl nuclear accident	Day et al. (1995), Worgul et al. (2007)
Medical workers	Worgul et al. (2004), Chodick et al. (2008), Kleiman et al. (2009), Vaňo et al. (2010)
<i>Studies questioning lower or zero threshold</i>	
Diagnostic procedures	Hourihan et al. (1999)
Radiotherapy	Chmelevsky et al. (1988)
Nuclear plant workers	Voelz (1967), Guskova (1999), Mikryukova et al. (2004), Okladnikova et al. (2007)

controversial, although some experimental and animal data do suggest that such preclinical radiation-induced lens opacities may progress with time to demonstrable visual disability.

Atomic bomb survivors

(270) A report that examined dose response and threshold in atomic bomb survivors who had cataract surgery is of great interest (Neriishi et al., 2007). These findings were the first to document clinically relevant visual disability many years after exposure to low-dose radiation. The authors reported a significant dose–response increase in the prevalence of cataract surgery, with an OR at 1 Gy ($OR_{1\text{Gy}}$) of 1.39 (95% CI 1.24–1.55) and no indication of upward curvature in the dose response. An analysis for the dose threshold showed a best estimate of 0.1 Gy (95% CI <0–0.8 Gy) after adjustment for age, gender, diabetes, and other potential confounders. This is significantly lower than the current estimates of 5 Sv (ICRP) and 2 Sv (NCRP) for visually disabling lens changes. It should be noted that at the time of the study (2000–2002), the youngest atomic bomb survivors were only 55 years old, while the average age for cataract surgery was ~73 years old, suggesting that additional surgical cases may occur in future years. The authors noted that their data were incompatible with a dose threshold of >0.8 Gy.

(271) It is important to recognise that these findings are comparable with, and in support of, earlier studies of lens opacification in atomic bomb survivors who had not had cataract surgery, and which utilised more subjective slit-lamp examinations to evaluate radiation-related lens changes in the exposed populations. An early study by Otake and Schull (1982) used cataract data 19 years after the atomic bomb to calculate a threshold dose estimate of 1.5–2.0 Sv for cataract development.

(272) More recently, Minamoto et al. (2004) reported examination of 913 individuals from 2000 to 2002, mostly including persons who were aged <13 years at the time of the bombings. Slit-lamp and retro-illumination examinations of individuals aged 54–94 years (mean 64.8 years) from both Hiroshima and Nagasaki were completed and graded according to LOCS II methodology. Doses were based on DS86 dosimetry. A significant increase in cortical and PSC cataracts was reported with increasing radiation dose adjusted for city, age, gender, and smoking. A significant difference between Hiroshima and Nagasaki atomic bomb survivors in terms of cataract prevalence prompted a further recent analysis that incorporated the variable impact of UV light on the eye (Minamoto et al., 2011). The results suggested that cataracts among Nagasaki residents were more frequently located at the inferior nasal portion of the lens compared with cataracts in Hiroshima residents, with no ionising-radiation-specific localisation observed. Models of city differences in terms of UVA and UVB levels showed that the UVB model provided a better fit than the UVA model, suggesting that UVB might account for the city difference. The current study implicated the geographical location of the subject, the investigation period, and outdoor activities as potentially important surrogate factors for UVB influences in radiation-induced cataracts.

(273) In 2006, further re-analysis of digitised lens images using newer DS02 dosimetry and separation of the subjects irradiated in utero revealed a best estimate of

threshold dose of 0.6 Gy (90% CI <0–1.2) for cortical cataracts and 0.7 Gy (90% CI <0–2.8) for PSC cataracts (Nakashima et al., 2006). It should be noted, however, that atomic bomb survivor studies provide epidemiological support for a low or zero threshold in acutely exposed populations, but do not provide data for chronically exposed populations.

Chernobyl accident liquidators

(274) Lens examinations of those exposed as a result of the Chernobyl nuclear accident have provided important epidemiological data for protracted, low-dose exposures of similar magnitudes as those received by atomic bomb survivors. This is especially important given that considerable animal and human data indicate that dose fractionation of low-LET radiation results in significant reduction in cataract prevalence (Merriam and Focht, 1962; Di Paola et al., 1978; Worgul et al., 1989).

(275) Findings from the Ukrainian/American Chernobyl Ocular Study (UACOS) (Worgul et al., 2007) lend additional support for a lowered cataract threshold. This longitudinal study of cataract onset and progression in 8607 liquidators, responsible for the clean-up of radioactive materials after the accident, used conventional slit-lamp biomicroscopy of carefully selected subjects with well-documented low-dose exposures 12 and 14 years after the accident. Participants, almost exclusively males, had an average age of 33 years at exposure and thus were at low risk for any type of pre-existing lens opacification. At the first examination, 12 years after exposure and at an average age of 45 years, a 30% prevalence of precataractous changes was noted with a 20% prevalence for Stage 1 opacification. While not visually disabling, these early lens changes in a relatively youthful population at low risk for cataract development suggest that the small doses to which most liquidators were exposed had already started to cause precataractous lens changes. Confounding variables, including age, smoking, diabetes, corticosteroid use, and occupational exposure to hazardous chemicals or UV radiation, were included in the analysis.

(276) Stage 1 opacities demonstrated a dose response for both PSC ($OR_{1Gy} 1.4$, 95% CI 1.0–2.0) and cortical opacities ($OR_{1Gy} 1.5$, 95% CI 1.1–2.1). Data for more advanced opacities (Stages 2–5) were also suggestive of an elevated risk ($OR_{1Gy} 1.8$, 95% CI 0.9–3.7) but were not significant, perhaps because of the relatively small numbers of individuals who had progressed to these stages. No dose association for nuclear cataracts was noted ($OR_{1Gy} 1.07$). When Stage 1 PSC and cortical cataracts were analysed for dose thresholds, they both yielded best estimates of the dose threshold of approximately 0.35 Gy, and the CIs excluded values of >0.70 Gy. These findings do not support the current guidelines of a 5-Gy threshold for detectable opacities from chronic exposure, and further suggest a dose–effect threshold of <1 Gy.

(277) Knowing that the latent period for radiation cataracts is inversely related to dose, continued follow-up of the UACOS cohort offers the opportunity to further refine the presumptive radiation cataract threshold. Also, as the average age of the liquidators is now only 53 years and 94% received exposures of <0.40 Gy, future ocular examinations over the next decades have the potential to provide more precise

statistical support for current or future estimated threshold values for radiation cataract.

Techa River studies and other similar installations in the former USSR

(278) It is difficult to obtain detailed information about ocular studies in subjects accidentally exposed as a result of operations at the Mayak plutonium production complex or other similar installations in the former Soviet Union. Several cohorts of exposed workers and residents of the Techa River region have been assembled, and ongoing health surveys and epidemiological investigations have been reported (Kossenko et al., 2005; Azizova et al., 2008). Findings of ocular health outcomes or development of radiation cataracts have not yet been reported from such studies.

(279) Nevertheless, some information is available in English language publications and meeting reports, as well as abstracts of Russian literature, concerning various ocular pathologies in exposed individuals. For example, an extended meeting abstract noted that ocular examinations were performed from 1951 to 1999 among approximately 30,000 individuals exposed to radioactive contamination while living alongside the Techa River System from 1950 to 1952 (Mikryukova et al., 2004). This study of 'visual disturbances' reported a wide range of ocular diagnoses in the subject population, and specifically noted that cataracts represented the most frequently diagnosed pathology, accounting for 26% of all cases. An attempt to make some estimates of ERR of all eye disease due to radiation exposure suggested a weak association. Individual risks for cataracts or any other specific ophthalmic disorder were not provided.

(280) More generally, a review of Russian medical findings from Mayak and other sites by Guskova (1999) made the statement that while acute exposures of 2–10 Gy often resulted in PSC cataracts with accompanying visual loss, chronic exposures of the same doses did not result in cataracts, visual disturbances, or eye pathology of any type. Specific types of exposure and/or individual cases were not delineated, nor were supporting references provided.

(281) One case of occupationally associated radiation cataract was reported among 37 cases of ARS at Mayak, in which the patients recovered from the initial acute effects of exposure (Okladnikova et al., 1994). The subject with cataract was reportedly exposed to a combination of gamma and neutron sources 35 years earlier with a total dose exceeding 3 Gy. The authors noted that no cases of radiation cataract were noted in any of 1828 subjects diagnosed with ChRS and who received total cumulative external doses of 0.5–8 Gy of gamma radiation (2–3 Gy/year maximum) or combined external gamma and internal ^{239}Pu contamination. These individuals were monitored for up to 35 years following exposure and received periodic comprehensive medical examinations. A number of subjects succumbed to various cancers and cardiac pathologies during the study period. Details of the ophthalmic examinations were not provided.

(282) In contrast, three cases of radiation cataract were noted in Mayak workers exposed to neutron radiation and who experienced ARS (Mikhailina and Vinogradova, 1992). An additional bilateral case of blinding cataract was reported in a

woman acutely exposed to 7–12 Gy neutrons and who developed visual symptoms years later (McLaughlin et al., 2000; Azizova et al., 2005). Curiously, a later report concerning the availability of tissue specimens from 700 deceased Mayak workers noted that occupational cataracts were seen in six cases, three of which included individuals with ChRS and one which included a patient with occupational lung fibrosis (Muksinova et al., 2006). No further details concerning cataract type, latency, visual disability, range of exposures, or other details were provided. This report is in contrast to the earlier publication from Okladnikova et al. (1994), which stated that none of the subjects with cutaneous radiation syndrome in that study had radiation cataracts. It is difficult to compare the two studies without additional information about the study populations.

(283) A review of long-term medical complications in workers employed at the world's first nuclear power plant, APS-1 Obninsk (Atomic Power Station 1 Obninsk), suggested that radiation cataracts were only noted in acutely exposed workers (>4 Gy) (Okladnikova et al., 2007). No specific details were provided.

(284) In the Russian studies, while radiation cataracts have been noted in individuals acutely exposed to radiation of >2 Gy of various qualities, none of the published findings suggest that chronic or low-dose exposure is associated with visual disability and/or radiation cataracts. It is difficult to reconcile these studies with the various recent works in the West, other than to say that the definition of radiation cataract and visual disability may differ (with the Russian studies defining a much more severe visual disability), and/or the methods for ocular examination, verification of radiation cataracts, and ultimate diagnosis may be significantly different.

Radium exposures

(285) A case report of radiation cataract described histological and morphological analysis of both lenses removed from an individual exposed to an improperly shielded radium source 26 years earlier (Hayes and Fisher, 1979). This manuscript is unusual in its detailed light and electron micrographic description of the morphology of a human radiation cataract.

(286) For 11 years, this subject was irradiated for a few minutes, three times each week, by a radium source of 120 mg. No other exposure details (e.g. distance, shielding arrangement) are provided. Nevertheless, the case study provides some information concerning radiation cataract latency given the long time between last exposure and the need for cataract extraction almost three decades later. A maximum potential dose could be calculated with a worst-case scenario positioning an unshielded radium source within 12 inches of the subject's eyes. Slit-lamp examination of this individual's eyes revealed characteristic subcapsular opacification in both the anterior and posterior lens regions. Unfortunately, no information about lens changes prior to extraction is provided, so the temporal relationship between the anterior and posterior changes is unclear. Of interest, a region of central posterior opacification is noted some 250 μm anterior to the posterior pole, and the authors suggested, based on measurement of axial distance and human lens growth rates, that this region corresponds to lens fibre cells improperly formed some 30–35 years earlier.

The authors also suggested that the histological appearance of the lens, which includes abnormally differentiated epithelial cells, lends further support to the theory that radiation cataracts arise from the improper division and differentiation of irradiated lens epithelial cells.

(287) In comparison with the previous study documenting radiation cataracts following brief but chronic external (low-LET) radium exposure, Chmelevsky et al. (1988) reported radiation cataracts arising in a population therapeutically treated with ^{224}Ra for tuberculosis and ankylosing spondylitis some 20 years earlier. Due to the nature of the Ra source, lenses were primarily exposed to alpha particles, and there are large uncertainties associated with dose estimates (Taylor et al., 1988). Cataract incidence was compared with initial injected activity/kg body weight. Due to uncertainties regarding Ra uptake and metabolism in ocular tissue, including permeability of the lens capsule to Ra and the specific absorbed dose to the lens epithelium, accurate determinations of lens dose cannot be made. Nevertheless, the authors reported that a significant and increasing percentage of individuals reported visual disability, and that the majority of lens opacities were bilateral: 58 cases were reported, 25 of which occurred before 54 years of age, and 42 cases resulted in documented cataract surgery. The study relied on reporting from the individual patient's medical record and/or communication with their ophthalmologist. Independent slit-lamp examinations were only made in 11 cases, although PSC cataracts were documented in the majority of these cases. The authors reported that the majority of cataracts diagnosed at early ages occurred mainly at higher dosages. Based on segregation of the data into early and late diagnosis, they suggested that the data were only compatible with a linear dependence on dose beyond an initial threshold exposure. There was little correlation between dosage and age at diagnosis beyond 60 years of age. The authors concluded that their data were most compatible with a deterministic view of radiation cataracts with a threshold of the order of 0.5 MBq/kg body weight. This conclusion is undermined, however, by the lack of classification of cataracts into cortical, nuclear, and PSC types, and the inclusion of what are presumably age-related opacifications unrelated to exposure in the study population.

Paediatric populations

(288) The UACOS findings are also supported by results of a study of lens changes in a paediatric population exposed as a result of the Chernobyl accident (Day et al., 1995). Estimates of cumulative dose ranged from 0.029 to 0.086 Sv. A small but significant increase in the incidence of subclinical PSC lens changes (3.6%), greatest among males aged 12–17 years at the time of examination, was noted in ~1000 exposed children, compared with a matched population of ~800 unexposed subjects. It should be noted, however, that dose estimates contain large inherent uncertainties; for example, individual dose estimates were not determined but were instead based on recorded environmental exposure levels. The authors also noted that the ophthalmologists were not blinded as to the identity of the exposed and unexposed subjects, as exposed children were mainly defined by the environmentally contaminated villages where they currently lived.

To minimise potential observer bias, the study included examination by two independent ophthalmologists. The authors also noted that population migration after the disaster may have affected the results in unknown ways as the exposed population was selected from those who resided in formerly contaminated areas at the time of the ophthalmic examinations, and thus did not represent a random sampling of all children exposed at the time of the accident. On the other hand, the presence of PSC defects of a type consistent and characteristic of ionising radiation exposure and not normally found in a paediatric population is suggestive of cause and effect. If additional support for continued ophthalmological examinations and better dose reconstruction in this cohort is forthcoming, a well-designed epidemiological study has the potential to provide additional statistical support for these findings.

(289) In another exposed paediatric population (Hall et al., 1999), the prevalence of lens opacities in 484 adults who were treated as infants (<18 months old) with external x-ray or radium therapy to treat haemangiomas of the head, face, or neck, was compared with that in a control population of 89 unexposed, age-matched individuals who presented with skin haemangiomas as infants but were not treated with ionising radiation. LOCS II criteria were used and lens dose was estimated based on patient treatment records and photographs, type of radiotherapy (flat applicators, type and number of externally placed tubes or needles, or x-ray treatments), and experimental lens absorbed dose calculations using a phantom. These individuals were treated between 35 and 54 years earlier, and exposed subjects received an average of two treatments with a cumulative mean dose of 0.4 Gy (median 0.2 Gy, maximum 8.4 Gy). Lens opacities of any type were found in 37% of exposed subjects compared with 20% of controls. A dose-response relationship was noted regardless of age at exposure. When corrected for age at examination, dose rate, and steroid use, the authors reported an OR_{1Gy} of 1.50 (95% CI 1.15–1.95) for cortical opacities and an OR_{1Gy} of 1.49 (95% CI 1.07–2.08) for PSC opacities. In contrast, no dose-response relationship was noted for nuclear lens changes. Overall, uncorrected ERR for cortical or PSC opacities in those exposed as infants was 1.35 (95% CI 1.07–1.69) and 1.50 (95% CI 1.10–2.05), respectively.

(290) Another screening study of 20 individuals 30–45 years after being treated for skin haemangioma in infancy noted precataractous subcapsular lens changes in the eyes on the untreated side of the face, where lens doses were estimated to average 0.1 Gy (Wilde and Sjostrand, 1997).

(291) A study of a paediatric population accidentally exposed while living in a ^{60}Co -contaminated apartment indicated an OR_{1Gy} of 1.18 for non-clinical lens changes (Chen et al., 2001b). Mean exposure of 0.17 Gy (with median value of 0.054 Gy, personal communication from Dr. Muh-Shy Chen) was noted in this population, although doses ranged widely from 0.001 to 1.2 Gy. Annual ^{60}Co exposures of >0.005 Gy/year, in some cases for >10 years, were reported. A recent follow-up of some of these children after a second ophthalmology examination, all still <23 years of age, indicated that radiation-induced lens changes, measured as subclinical FLD, continued to increase in size and number several years after

relocation from the contaminated site (Hsieh et al., 2010). The authors noted a positive relationship between cumulative ^{60}Co dose and the sum of posterior and anterior FLD scores, although the increase in anterior cortical lens FLD scores was greater than that of posterior FLD scores. The progressive nature of such changes 5 years later, in a paediatric population now removed from the contaminated environment, supports the earlier findings of radiation-associated lens changes in this population, and demonstrates that such radiation-induced lens changes may persist and progress with time. The authors indicated that the estimated average cumulative exposure of ~ 0.2 Gy (median 0.054 Gy) for observing an increase in total FLD score 5 years later was well within the range of reported threshold doses for radiation cataract.

Patients treated for Tinea capitis

(292) In the first half of the 20th Century, before the development of modern antifungal medications, ringworm of the scalp (*Tinea capitis*) was often treated by epilation using x-ray doses ranging from 3.0 to 3.8 Gy (Shore et al., 2003), up to 6 Gy (Ron et al., 1991), and as high as 8.5 Gy to the scalp (Shore et al., 2003). As many as 200,000 individuals may have been irradiated worldwide (Cipollaro et al., 1959; Shore et al., 1976). A variety of health effects and pathologies were documented in the following decades in a number of cohorts, most notably in $\sim 11,000$ Israeli immigrants (e.g. Modan et al., 1977; Ron et al., 1988) and ~ 2000 young children irradiated at New York University Hospital between 1940 and 1959 (Schulz and McCormick, 1968; Albert et al., 1968; Shore et al., 1976). Despite the fact that the patients' eyes were often shielded with lead foil, recreation of the original treatment procedures indicated that the lens received doses ranging from 0.2 to 0.8 Gy (Schultz and Albert 1968; Harley et al., 1976). Differences in children's head sizes and lack of precise positioning in the x-ray field probably accounted for some variability in exposure.

(293) From 1964 to 1965, approximately 15 years after treatment, an increased incidence of early posterior lens changes, characteristic of ionising radiation exposure, was noted after slit-lamp examination of treated subjects (Albert et al., 1968; Shore and Worgul, 1999). While the overall severity of such changes was minor, the authors noted a 'pronounced increase' in capsular opalescence or sheen as well as an accumulation of bright dots or micro-opacities, likely corresponding to Merriam-Focht Stages 0.5–1.0. Thirteen cases of 'posterior subcortical' opacities were noted in exposed individuals compared with two cases in unirradiated controls. An estimated OR of 5.9 was calculated (Shore and Worgul, 1999). A second follow-up from 1968 to 1973, based on a mail survey approximately 25 years after exposure, did not detect any difference in cataract incidence between exposed individuals and controls (Shore et al., 1976). Unlike the previous detailed ocular examination, which may have detected early radiation-associated lens changes unaccompanied by visual disability, the later survey asked respondents to self-report on any subsequent cataract diagnosis, surgery, or associated visual disability. This could account for the differences in outcomes between the two studies.

US radiation workers

(294) Jacobson (2005) reported an increased incidence of PSC opacities in retired nuclear plant uranium processing workers at three US Department of Energy facilities. Cataract type was documented by telephone interview with each person's ophthalmologist, while transuranic body burdens from 0 to 0.6 Sv were calculated from individual dosimetric records maintained by each installation. There were 97 subjects with a median age of 76 years in the study, and 20.6% of these were reported to have PSC cataracts (most were bilateral). The median recorded dose for all cases was 0.168 Sv, compared with 0.089 Sv for subjects without PSC cataracts. A significantly higher number of cases was noted for subjects exposed to >0.2 Sv (37.5%) compared with lower exposures (15.1%).

(295) In contrast to this study, a much earlier study by Voelz (1967) of ~850 nuclear reactor workers of relatively young ages (<40 years) occupationally exposed to low doses of gamma and/or neutron radiation over a 15-year span, concluded that visual disability was not associated with exposure and that no radiation cataracts were detected in this cohort. Unfortunately, no further long-term follow-up of these workers has been reported. Maximum reported individual exposure (gamma and neutron) was 25 rem (0.25 Sv) with a mean of 4 rem across all age groups. Of note, minor lens changes (PSC opacities, vacuoles, and polychromatic plaques) that did not affect vision were described in 10–36% of individuals with strong age-related dependence. The mean cumulative exposures in subjects with these findings were no different from those without such changes, and the author concluded that these represent ageing and not radiation effects. The dosages to which these workers were exposed were considerably lower than those in the later Jacobson study (Jacobson, 2005), and the average age at examination was some 20 years younger. Therefore, comparisons between the two groups are difficult.

(296) An interesting case report described both clinical and histological features of a posterior cataract in a 47-year-old worker at an undefined nuclear facility (Griffith et al., 1985). Described as a 'process worker', he was potentially exposed to external beta, gamma, and fast neutrons, as well as inhalation hazards from plutonium. His recorded film badge showed that his total occupational whole-body dose was 67 rem and dose to the lens of the eye was 70–87 rem. His work history included a number of incidents in which his hands or face were contaminated with 'small' amounts of plutonium which were promptly treated and removed. Urinary excretion measurements indicated a body burden of 2 nCi the year prior to his cataract diagnosis. Based on ICRP guidelines at that time, the authors concluded that his external exposure was below threshold limits for radiation cataract development, and noted that his ²³⁹Pu body burden was also well within occupational exposure limits. As an alternative explanation, based in part on animal studies, the authors hypothesised that ²³⁹Pu was preferentially retained in the iris and ciliary body, in close contact to the lens, and that this exposure was the contributory factor in his cataract development.

Astronauts

(297) Data from the US astronaut corps (Cucinotta et al., 2001; Rastegar et al., 2002) and military aviators (Jones et al., 2007) are also suggestive of a relationship between low-dose radiation exposure and earlier onset and increased prevalence of cataracts, although the quality and energies of space radiation exposures are fundamentally different from those occurring on Earth.

(298) Most recently, Chylack et al. (2009) reported preliminary results from the NASA Study of Cataract in Astronauts survey. The purpose of this ongoing work is to examine potential relationships between space flight, ionising radiation exposure, radiation cataract prevalence and/or progression, and various co-determinants of risk and/or radioprotection. Preliminary baseline findings were presented in the study cohort. The survey was designed to compare lens findings in a cohort of 171 US astronauts that had flown in space with a well-matched control population of 247 astronauts and/or military aviators that had not flown such missions. Of concern, only approximately 60% of the astronauts with documented or likely exposure to high-LET radiation were included in the study. Most participants were involved in shuttle missions in low Earth orbit, and were less likely to receive significant cataractogenic doses or to be exposed to potentially more damaging heavy ions.

(299) Radiation-associated lens changes were documented by LOCS III (Chylack et al., 1993) criteria using primarily automated densitometric measurements of retro-illumination lens images, which may not detect minor focal opacities and posterior capsular changes. In most cases, the reported change in overall density was close to background levels.

(300) The authors reported that the variability and median number of cortical cataracts were significantly higher for exposed astronauts than for non-exposed astronauts and comparison subjects of similar age ($P = 0.015$). Baseline findings also indicated that space radiation was positively associated with increased 'PSC area' ($P = 0.015$) and focal centres ($P = 0.056$). A dose relationship between PSC size and exposure was noted in the astronaut core. Nuclear cataracts were not associated with space radiation exposure. The authors concluded that cataract risk for cortical and PSC opacities may be increased at small radiation doses.

Medical workers and interventional radiologists

(301) UNSCEAR (2000) reported that exposure of interventional medical workers and radiological technicians to x rays is the greatest source of occupational exposure in medicine. With respect to interventional medical procedures using fluoroscopy, practitioners may be exposed to a relatively high ocular dose of x rays over the course of a career (Kim et al., 2008; Vañó et al., 2008; Ubeda et al., 2010). With an exponential increase in invasive radiological, cardiological, and urological procedures (UNSCEAR, 2000), it is intriguing to speculate whether such specialists, for whom eye protection has only recently been recommended, are more likely to develop lens opacification as a result of their normal workload. It is already clear that personnel in interventional suites may develop

cataracts when inadequate radiation protection is provided (Vañó et al., 1998). Several studies in these groups of occupationally exposed individuals offer support for this hypothesis.

(302) A pilot study of interventional radiologists aged 29–62 years reported that the prevalence and severity of PSC cataracts were associated with age and years of practice (Junk et al., 2004). Reconstructed annual dose estimates of lens exposure ranged from 0.45 to 0.90 Sv. These exposures are consistent with reported exposures of similar medical workers (Vañó et al., 2006; Kim et al., 2008). Nearly half of those examined (22/59) had early lens changes (posterior dots and vacuoles) associated with radiation exposure, while five subjects had clinically significant PSC cataracts. However, there was no age-matched control group in this study, so the effects of ageing vs radiation exposure are unclear.

Interventional cardiologists

(303) X-ray exposure to the lens of the eye of interventional cardiologists and other paramedical personnel working in catheterisation laboratories is high, and could result in radiation-induced lens changes. A recent pilot study to investigate this was organised by IAEA (Kleiman et al., 2009; Vañó et al., 2010). The study included a detailed questionnaire regarding exposure history as well as a comprehensive dilated slit-lamp examination among a cohort of interventional cardiologists, nurses, and technicians working in cardiac catheterisation laboratories, as well as in a control group of non-medical professionals. Of 116 exposed individuals, PSC opacities were found in 38% of cardiologists and 21% of paramedical personnel compared with 12% of controls. None of the individuals with lens opacities had operable, visually disabling lens changes, but the progression of such defects is typically slow. Cumulative occupational mean lens doses were estimated at 6.0 Sv for cardiologists and 1.5 Sv for associated staff when eye protection was not used. The RR of PSC opacities in interventional cardiologists, compared with unexposed controls, was 3.2 (95% CI 1.7–6.1, $P < 0.005$). While the interventional cardiologists were, on average, some 5 years older than the controls (46 vs 41 years), the observed 300% difference in RR is unlikely to be attributed to age because only a very modestly increased age-related risk for PSC cataracts has been noted in the literature, and PSC cataracts only represent a small fraction of lens opacities at any age.

(304) A similar study in a Malaysian cohort (Ciraj-Bjelac et al., 2010) reported a strong dose–response relationship between occupational x-ray exposure and detectable posterior lens changes in interventional cardiologists. A dose–response relationship for nurses was not reported due to the smaller sample size of nursing staff. A significant difference in the prevalence of posterior lens opacities was noted for cardiologists [29/56 (52%), $P < 0.001$] and nurses [5/11 (45%), $P < 0.05$] compared with age- and sex-matched unexposed controls (2/22, 9%). RRs for lens opacification were 5.7 (95% CI 1.5–22) for cardiologists and 5.0 (95% CI 1.2–21) for nurses. Mean cumulative estimated lifetime occupational doses to the lens of the eye were reported as 3.7 Gy for cardiologists (range 0.02–43 Gy) and 1.8 Gy for nurses (range 0.01–8.5 Gy).

(305) The authors of both publications suggested that the use of eye protection would be prudent for individuals working in interventional cardiology to delay progression and limit future cumulative dose to the lens. Future well-designed epidemiological studies in similar but larger groups of interventional medical professionals with well-documented exposures and long work histories may provide additional support for these hypotheses.

Radiological technologists

(306) A well-designed, prospective analysis, with 20-year follow-up, of 35,700 radiological technicians, 22–44 years old at the start of the study, assessed the risk for lens opacification and/or cataract surgery by means of a follow-up questionnaire (Chodick et al., 2008). Cataract diagnosis or surgery was self-reported by the respondents. A number of potential confounders, such as estimated sun exposure, obesity, diabetes, hypertension, and arthritis, were also analysed. The study results indicated that having 10 or more diagnostic x rays, particularly to the face or neck, was significantly associated with increased risk of cataracts. Protracted occupational exposure to low-dose ionising radiation was marginally associated with elevated risk of cataract diagnosis. Workers with the highest reported exposures to the lens (mean 0.06 Gy) had an adjusted HR of 1.18 (95% CI 0.99–1.40) compared with individuals in the lowest category of occupational lens exposure (mean 0.005 Gy), although the dose–response trend was not statistically significant. The median occupational radiation dose to the lens was estimated to be 0.028 Gy for the entire cohort. Significantly, the association between radiation exposure and self-reported cataract was strongest among technologists diagnosed before 50 years of age. Subcapsular cataracts are more likely to be associated with a younger age of onset; therefore, this finding may provide some additional information regarding low-dose exposure and PSC cataract development in these individuals. However, it is noted that no significant associations were seen for cataract extraction incidence.

Conclusions

(307) In summary, recent human epidemiological findings for acutely, protractedly, and chronically exposed populations suggest that the current ICRP guidelines following fractionated or prolonged exposures of a 5-Gy threshold for detecting opacities and an 8-Gy threshold for visual impairment (ICRP, 1991a, 2007) may underestimate risk. Some of the earlier epidemiological studies, on which these recommendations were made may not have had sufficient follow-up to detect either radiation-induced lens changes or visual disability requiring cataract surgery. In addition, better techniques for detecting, quantifying, and documenting early radiation-associated lens changes, as well as better dosimetry, may be factors that contributed to more recent findings of radiation cataract risk at low exposures. Continued follow-up of atomic bomb survivors, Chernobyl victims, and various occupationally exposed individuals may lead to a more precise estimate of any threshold.

2.6.4. Experimental data and mechanisms of damage

Animal models for radiation cataracts

(308) Studies with animals offer the opportunity to examine the effects of precisely controlled radiation exposures on specific pathologies. One such model utilizes development of radiation cataracts in rodents as a way to examine radiosensitivity (Schenken and Hagemann, 1975; Worgul, 1986; Brenner et al., 1996). Thus, cataractogenesis provides an experimental endpoint to study radiation effects in a late-responding normal tissue (Worgul et al., 2002). As an added benefit, such studies may provide additional insights into the large and growing worldwide societal health issues concerning cataract-related blindness (WHO, 2004).

(309) Animal studies are well suited to examine the relationship between radiation and cataract development at both tissue and cellular levels. These model systems have great relevance to human radiation exposure and subsequent health outcomes. Extension of the presumed radiation cataract threshold in animal models to even lower doses is likely to be important to the development of appropriate guidelines for national radiation risk policy.

(310) Recent findings demonstrate dose-related significant lens opacification within a reasonable fraction of the life span of the mouse or rat after exposure to as little as 0.10-Gy x rays or 0.325-Gy ^{56}Fe (Worgul et al., 2005a,b). For example, 4-week-old rats were irradiated with doses of either 0.1 or 0.5 Gy of 250-kVp x rays, and lens changes were followed by weekly slit-lamp examination for 64 weeks (~35% of average life span) using a modified Merriam–Focht radiation cataract scoring method (Fig. 2.9). Sixty-four weeks after exposure, more advanced cataracts (Stages 1.5 and 2.0) were just beginning to appear in the 0.5-Gy whole-lens-irradiated group, with a prevalence of 0.1.

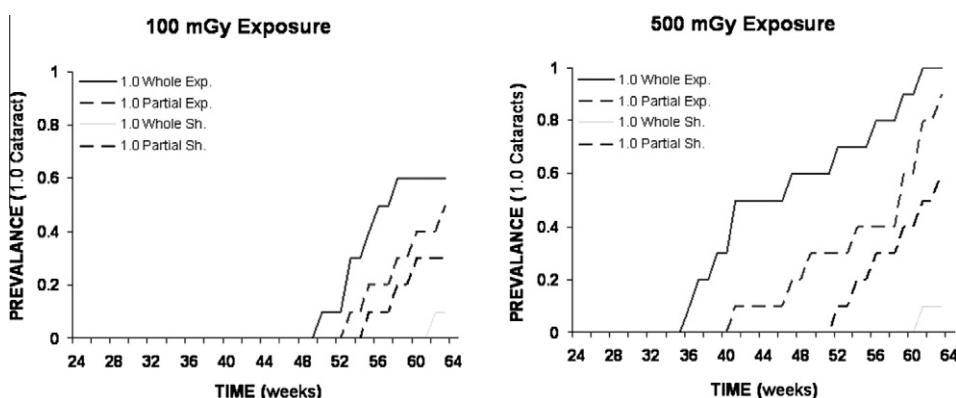


Fig. 2.9. Prevalence estimates as a function of time following irradiation for Stage 0.5 and 1.0 cataracts following irradiation with 0.1 or 0.5 Gy. The figures show early opacification in lenses totally exposed without any lead shielding (Whole Exp.), totally shielded lenses (Whole Sh.), and the shielded (Partial Sh.) and unshielded (Partial Exp.) portions in half-shielded lenses (Worgul et al., 2005a).

(311) This animal study used doses far lower than the presumptive threshold dose for cataracts. The fact that 0.1 Gy of x rays is cataractogenic within one-third of the life span of the rat is important and relevant, given that the rat radiation cataract model is very similar to human lens opacification. An example of particular relevance to human regulatory guidelines and risk estimates is that the generally presumed threshold of 2 Sv for cataract development in the rat (based on short-term studies) mirrors that which is currently considered the threshold in humans. These findings establish that a dose of 0.1 Gy of x rays produces measurable lens opacification within one-third of the life span of the rat, and suggests that lower doses may also be cataractogenic.

(312) Animal models are also important in helping to determine the pathology, molecular mechanisms, and biochemistry underlying radiation cataract (Blakely et al., 2010). For example, a mouse model was recently employed to demonstrate specific DNA damage, and an apparent association between the persistence of oxidatively induced DNA adducts and aberrant lens epithelial cell differentiation and migration following x-ray exposure (Wolf et al., 2008). In addition, radiation-induced changes in lenses in frogs have been studied using high doses (Holsclaw et al., 1989, 1994). However, the findings of restoration of fibrogenesis and non-progressing lesions at 10 Gy but not at 25 Gy, pointing to qualitative differences in lesions as a function of dose, were not found in rodents using lower doses.

(313) In a similar fashion, for >40 years, the role and contribution of dose fractionation to radiation cataract development has been examined in great detail in the animal eye (Merriam and Focht, 1962; Jose and Ainsworth, 1983; Worgul, 1988; Brenner et al., 1996).

(314) More recently, in a series of papers, the contribution of gender and sex hormones to radiation cataract development and the possibility of both negative and positive radioprotective effects of oestrogen in ⁶⁰Co gamma-irradiated rat eyes has been described (Dynlacht et al., 2006, 2008; Bigsby et al., 2009; Henderson et al., 2009). In addition to providing useful information concerning potential gender-based radiation cataract risk, such studies may prove useful in understanding the biology underlying epidemiological data suggesting that the age-adjusted risk for cataracts is significantly greater for females than for males (EDPR Group, 2004; Klein et al., 2008).

(315) Animal radiation cataract models have also proved to be of great utility in demonstrating the potential efficacy of various potential radioprotectors (see Section 3.3.6).

Mechanisms of damage

(316) It is generally assumed that ionising radiation exerts its cataractogenic effect in the lens epithelium (Hanna and O'Brien, 1963) through genomic damage (Worgul et al., 1991), with resultant mutation and/or misrepair in lens epithelial cells that do not immediately die following irradiation (Worgul and Rothstein, 1975; Jose, 1978; Worgul et al., 1989). Although the precise mechanisms of radiation cataracts are not known, genomic damage resulting in altered cell division, transcription, and/or abnormal lens fibre cell differentiation is considered to be the salient injury, rather

than cell killing which becomes apparent at high doses (Holsclaw et al., 1989). Radiation cataract formation is, a priori, dependent on survival and potential division and/or differentiation of lens epithelial cells with compromised genomes (Worgul and Rothstein, 1977; Worgul et al., 1989, 1991). It is postulated that aberrantly dividing and/or differentiating cells in the pre-equatorial region of the lens epithelium migrate, predominately to the lens posterior pole, where they become opaque lens fibres (Worgul et al., 1991; Kleiman, 2007; Blakely et al., 2010).

Molecular and cell biology

(317) Lens organ and epithelial cell culture models play an important role in understanding the biochemical, cellular, and molecular sequence of events leading to radiation-induced lens fibre cell opacification (Blakely et al., 2010). For example, radiation-induced defects in cell signalling, various growth factors including fibroblast growth factor (FGF) and cyclin dependent kinase (CDK) (Chang et al., 2005, 2007), extracellular matrix protein production (McNamara et al., 2001; Chang et al., 2007), and the role of cell death and apoptosis (Belkacemi et al., 2000) may play important roles in determining future aberrant epithelial cell division, differentiation, and fibre cell migration.

Genetic susceptibility

(318) Radiation cataract formation is likely to be dependent on survival and potential division and/or differentiation of lens epithelial cells with compromised genomes (Worgul et al., 1989). Thus, radiation-induced unrepaired DNA damage in such dividing and differentiating lens epithelial cells may be the crucial first step in cataractogenesis. Lenses containing cells with impaired ability to recognise and repair such damage are probably at increased risk for cataractogenesis. It has been suggested that heterozygosity for genes involved in cell-cycle checkpoint control, DNA damage recognition, or DNA repair might also contribute to this phenomenon via differential radiosensitivity (Andreassen, 2005; Hall et al., 2005).

(319) Risk estimates for damaging radiation effects have historically assumed that the human population is generally homogeneous in radiosensitivity. These risk assessments include ground-based radiation protection standards, radiation protection for space flight, and radiotherapy protocols. Recent findings in human epidemiological studies and animal models, however, suggest that there are radiosensitive subpopulations. This includes the recently reported increase in cataract prevalence in mice haplo-insufficient for both *ATM* and *MRAD9* (Kleiman, 2007).

(320) Inclusion of such radiosensitive subpopulations in human epidemiological studies may distort the shape of the dose–response curve, such that a linear extrapolation from high to low doses may be invalid. In addition, it is unethical and unwise to put radiosensitive individuals in situations where they might receive a large dose. Individuals that are haplo-insufficient for multiple genes involved in DNA damage repair and/or cell-cycle checkpoint control may be more susceptible to the cataractogenic effects of ionising radiation than wild types or those haplo-insufficient for only one such gene.

Oxidative stress and cataracts

(321) Oxidative stress is believed to be a major early or initiating event in the development of cataracts induced by a variety of different agents (Matsuda et al., 1981; Worgul and Merriam, 1981; Babizhayev et al., 1988; Padgaonkar et al., 1989; Spector et al., 1993; Spector, 1995). In human lenses, oxidation of lens constituents is a common finding (Augusteyn, 1981; Bhuyan and Bhuyan, 1983; Spector, 1984). Experiments with lens organ and cell cultures have demonstrated that such stresses result in rapid metabolic and cellular changes similar to those observed in human cataracts (Zigler et al., 1989; Kleiman et al., 1990; Kleiman and Spector, 1993; Giblin et al., 1995; Spector et al., 1995, 1998). Changes in cellular redox potential, membrane function, mitochondrial viability, and DNA damage have been shown to be the earliest events following oxidative stress (Giblin et al., 1987; Kleiman et al., 1990; Spector et al., 1995; Giblin, 2000).

DNA damage and cataract

(322) As DNA is so easily damaged by oxidative stress or direct photochemical action of UV light, many investigators have suggested that unrepaired DNA damage to the lens epithelium ultimately results in cataracts (Bellows and Bellows, 1975; Jose, 1978; Courtois et al., 1981; Bloemendal, 1984; Rink, 1985; Spector et al., 1989; Worgul et al., 1989). Two major mechanisms are proposed: (a) damage to the central zone cells could result in failure of the epithelium to provide sufficient metabolic regulation of the underlying cortical fibre cells; and (b) damage or mutation in the germinative region, where defects in the dividing cell population would result in aberrant formation of new cortical lens fibre cells. The latter is believed to be most important with regard to the development of radiation-induced PSC opacification.

(323) Evidence for a relationship between DNA damage and cataractogenesis includes: (a) the demonstration of an increased frequency of micronuclei, a marker of genomic damage, in the epithelium of patients with cataracts (Worgul et al., 1991); (b) the increased frequency of DNA single-strand breaks in the epithelium of some patients with cataracts (Kleiman and Spector, 1993); (c) the relationship between low- or high-LET irradiation and the development of PSC cataracts (Worgul et al., 1976); and (d) the association between bilateral cataracts and human genetic diseases involving defects in DNA repair mechanisms such as: Cockayne syndrome (Nance and Berry, 1992); Photosensitivity Ichthyosis, Brittle hair, Intellectual impairment, Decreased fertility, Short stature syndrome PIBI(D) S (Rebora and Crovato, 1987); Rothmund-Thomson syndrome (Vennos et al., 1992); and Werner syndrome (Goto, 2001). The likely involvement of DNA damage in the early events surrounding cataractogenesis is further supported by the finding that one of the earliest markers of oxidative stress in lens organ culture experiments is DNA damage (Kleiman et al., 1990; Spector and Kleiman, 1992; Spector, 1995).

2.6.5. Summary

(324) New data from animal models and from exposed human populations suggest that lens opacities occur at doses far lower than those generally assumed

to be cataractogenic, and these observations are consistent with the presence of a small or non-existent dose threshold. Recent occupational findings in chronically exposed workers suggest long-term risk for cataracts and the need for eye protection even at low doses. Given that all national and international risk standards for ocular exposure are predicated on a relatively high threshold, current risk guidelines for ocular radiation safety require re-assessment. In addition, both human and animal radiation cataract studies may provide identifiable genetic, cellular, and pathological markers with which to study the effects of low-dose ionising radiation exposure non-invasively over long periods of time, with broad applicability to other tissues and organs where radiation effects are not as easily measured or quantified.

2.7. Respiratory system

2.7.1. Anatomical features and proliferative organisation

(325) The respiratory system includes nasopharynx, pharynx, larynx, trachea, bronchi, and lungs. Inspired and expired gases are transported from the nasopharynx via the conducting system of repeatedly dividing and narrowing airways, ending in blind-ended sacs called 'alveoli'. Alveoli are thin-walled structures, enveloped by a rich network of pulmonary capillaries. Alveoli constitute the bulk of the lung tissue and are the FSUs of the respiratory system, being the sites of gaseous exchange between the atmosphere and the blood.

(326) Respiratory epithelium undergoes progressive transition from pseudostratified, ciliated, columnar epithelium in the trachea to simple cuboidal epithelium in the bronchioles. Alveolar epithelia are predominantly type I pneumocytes (squamous cells), interspersed with larger type II pneumocytes (secretory) and connected by tight junctions. The capillary endothelium is non-fenestrated and is also linked by tight junctions. Smooth muscle layers are found beneath the mucosa, increasing in prominence towards the terminal bronchioles. Smooth muscle tone controls resistance to air flow and is modulated by the autonomic nervous system. Cartilage provides the supporting skeleton for the larynx, trachea, and bronchi, and prevents collapse of the airways during respiration.

(327) Gas exchange is between type I pneumocytes, basal membrane, and capillary endothelium. Type II pneumocytes produce surfactant that lowers the surface tension of the alveolar lining, and impedes the development of atelectasis and exudative effusion from vessels into the alveolar cavities. Surfactant, together with macrophages in the alveolar wall, also participates in local immune reactions. Alveoli are separated by interalveolar walls, which are composed of loose connective tissue with capillaries, collagen, and reticular fibres.

(328) Proliferation rates in the normal adult lung are very low, with a labelling index of <0.5% and turnover times for the alveolar epithelium of >4 weeks. However, irradiated mouse lung shows two waves of increased proliferation in the type II pneumocytes, with proliferation rates increased more than five-fold (Coggle, 1987). The early wave of proliferation (2–8 weeks after single doses of 10–12 Gy)

precedes the onset of functional damage, but coincides with increased release of surfactant from these cells. The second wave of proliferation coincides with the onset of pneumonitis, and is probably stimulated by depletion of type I pneumocytes.

2.7.2. Clinical data on therapeutic exposure doses

Clinical syndromes

(329) Toxicity in the respiratory system is fairly common after thoracic irradiation for cancer of the lungs, breast, and oesophagus, and haematological malignancies where large volumes of lung are irradiated. Clinical symptoms of acute radiation injury, which develop during the first 1–3 months after radiotherapy, include dyspnoea, cough, and fever, characterised as radiation pneumonitis. Symptomatic pneumonitis occurs in approximately 5–10% of patients irradiated for mediastinal lymphoma or breast cancer, with higher incidences in patients with lung cancer (McDonald et al., 1995; Mehta, 2005; Marks et al., 2010b). During this phase, there is exudation of proteins into the alveoli, infiltration of inflammatory cells, and epithelial desquamation. When tolerance doses are exceeded, pneumonitis may be very severe or even lethal. The acute pneumonitis phase may progress to late fibrosis of alveolar septa at 6–24 months after radiotherapy (Coggle et al., 1986; McDonald et al., 1995). The affected alveoli collapse and are obliterated by connective tissue. Fibrosis can also develop in patients without prior pneumonitis. Radiation lung fibrosis may be asymptomatic, but some deterioration in pulmonary function usually occurs as fibrosis progresses. Tidal volume decreases, and breathing frequency tends to increase, with a reduction in maximum breathing capacity. Chronic respiratory failure may develop, preceded by dyspnoea, reduced exercise tolerance, and cyanosis. In addition, the lung becomes very susceptible to invasion by micro-organisms and chronic respiratory infection.

(330) Chest radiographs and CT images are used to detect both radiation pneumonitis and fibrosis, with CT scans being most sensitive (Mah et al., 1986, 1987; Ikezoe et al., 1988). Such techniques identify changes in asymptomatic patients and demonstrate that radiation-induced structural defects (changes in tissue density) are very common, occurring in 27–40% of patients with breast cancer and >60% of patients with mediastinal lymphoma (McDonald et al., 1995). Scintigraphic techniques have also been used extensively to investigate functional changes (perfusion and ventilation) in irradiated lungs (Prato et al., 1977; Boersma et al., 1993; Marks et al., 1993). Perfusion defects are more common and occur earlier than ventilation defects, which supports the concept of the earliest radiation damage occurring in the capillary endothelium. Decreases in perfusion have been seen as early as 3 weeks after the start of radiotherapy, with maximum decreases after approximately 10–40 weeks.

Dose–response relationship

(331) The most important factors determining the development of radiation pneumonitis and fibrosis are total dose and the volume of irradiated lung tissue. There is also a significant time factor due to proliferation of type II pneumocytes with

estimated dose recovered of 0.5 Gy/day (Bentzen et al., 2000). Clinical data from TBI with bone marrow replacement in patients with leukaemia, or from half-body irradiation for control of pulmonary metastases, show that ED₁ for lethal pneumonitis is 7–8 Gy, with ED₅₀ of 9.3 Gy (Fryer et al., 1978; Keane et al., 1981; Van Dyk et al., 1981). This indicates a very steep dose response for lung damage after high-dose-rate, whole-volume irradiation. Low-dose-rate irradiation increases lung tolerance by 2–3 Gy (Keane et al., 1981).

(332) Fractionated exposure of the whole lung also leads to considerable sparing. This is consistent with the relatively low α/β ratio of approximately 3–4 Gy determined from both clinical (Van Dyk and Keane, 1989; Dubray et al., 1995; Bentzen et al., 2000) and animal studies (Herrmann et al., 1986; Parkins and Fowler, 1986; McChesney et al., 1989; Vegesna et al., 1989; Van Rongen et al., 1993). Clinically significant (symptomatic) radiation pneumonitis is uncommon in adults after total doses of <20 Gy in 2-Gy fractions, with ED₅ and ED₅₀ values of 17.5 and 24.5 Gy, respectively, for fractions of 1.8–2.0 Gy to the whole lung (Emami et al., 1991). Reduced lung volume may be seen in young children after lower doses to developing lung (Wohl et al., 1975; Benoist et al., 1982).

(333) For the complex 3D treatment planning regimes used in modern curative radiotherapy of solid tumours, there is non-uniform exposure of varying volumes of the lungs to a wide range of doses. To establish dose–response relationships for radiation damage after partial volume exposures, biological models have been used to consider the influence of fractionation schedule and to estimate the relationship between the 3D dose distribution and the probability of developing a complication (Emami et al., 1991; Martel et al., 1994). A common approach for comparison of different fractionation schedules is to convert the total dose given to each part of the lung to a normalised total dose, which is the total dose in 2-Gy fractions that is biologically equivalent to the actual delivered dose, according to the LQ model (Van Dyk and Keane, 1989; Newcomb et al., 1993). The complex 3D treatment plan is then summarised using a dose–volume histogram, which can be reduced to a single parameter and related to the NTCP. The most commonly used parameters for assessing dose–response relationships are mean standardised lung dose (e.g. Boersma et al., 1994; Kwa et al., 1998) and lung volume irradiated to >20 Gy (e.g. Marks et al., 1997; Graham et al., 1999; Kim et al., 2005). Such approaches have shown that mean lung doses of >18–20 Gy or a volume of >25% lung exposed to 20 Gy are associated with a steeply rising probability of clinical pneumonitis and reduced lung function (Fig. 2.10). Various other values for the volume exposed have also been shown to predict risk of pneumonitis, suggesting that there is not a sharp threshold below which risk is negligible (Marks et al., 2010a).

(334) A disadvantage of reducing 3D treatment plans to a single parameter for prediction of lung damage is that no account is taken of potential regional differences in lung sensitivity, or the inclusion of the heart in some radiation fields. There is experimental evidence that these factors can influence the dose–response relationship for radiation-induced decreases in lung function (Travis et al., 1997; Novakova-Jiresova et al., 2005; Van Luijk et al., 2005).

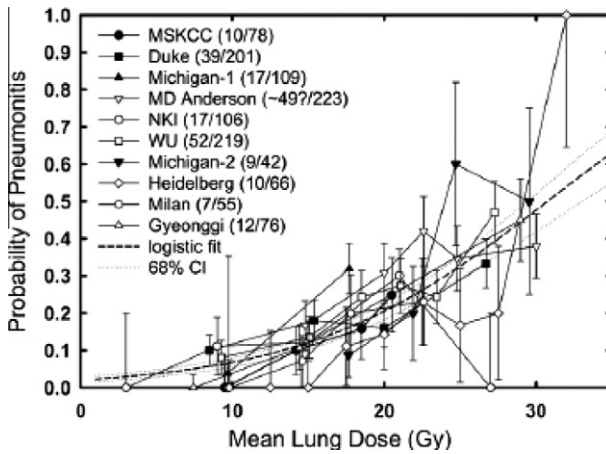


Fig. 2.10. Rate of symptomatic radiation pneumonitis after fractionated partial-lung irradiation related to mean lung dose. For full references of data used, see original Fig. 2 in Marks et al. (2010a).

(335) The relationship between radiation dose and structural lung damage has been studied extensively by Mah et al. (1987), and Van Dijk and Keane (1989). Well-defined curves for the incidence of patients with CT density changes $>5\%$ were obtained, with ED_{50} values of 33–34 Gy given in 2-Gy fractions. Combined CT and single photon emission computed tomography (SPECT) imaging can also be used to investigate the radiation dose–response relationship for regional changes in lung density, perfusion, and ventilation by precise matching of the local SPECT changes (per voxel) with contour-matched dose–volume distributions from the CT images. Logistic fits of dose–effect curves for 15% changes in local perfusion, ventilation, and density gave ED_{15} values of 31, 34, and 40 Gy, respectively, at 3–4 months after irradiation (Boersma et al., 1996). Partial recovery was seen at 18 months for perfusion and ventilation (ED_{15} values of 40 Gy), with somewhat less recovery for the parameter of lung density (ED_{15} 46 Gy). Such dose–response curves for local lung damage, unlike the response for total lung function, are largely independent of irradiated volume. This illustrates the point that the probability of a complication arising in organs with a parallel arrangement of FSUs, such as lung, is related to the number of FSUs destroyed and hence the volume of tissue exposed to high doses. The probability of destroying each FSU is, however, dependent on dose and not on the irradiated volume.

(336) Although radiation dose and treatment volume are the predominant factors determining radiation damage to the lungs, other treatment-related factors have been identified that contribute to the overall risk. Chemotherapy, especially regimes using concurrent bleomycin, doxorubicin, or cyclophosphamide, reduces the lung tolerance to radiotherapy (Hrafinkelsson et al., 1987; Lagrange et al., 1988; Seppenwoolde et al., 2003; Mehta, 2005). Experimental studies in mice indicate a substantial modifying effect, with dose modification factors (DMFs) of 1.5–2.4 for these drugs given concurrently with radiation (Von der Maase et al., 1986). Several

studies have investigated the relationships between patient-related factors (e.g. age, smoking, comorbidity) and biological parameters (levels of circulating cytokines, risk of damage), although results are not always consistent (Mehta, 2005).

(337) One particularly interesting debate surrounds the predictive value of plasma TGF- β levels in identifying patients most likely to develop lung damage after radiotherapy. TGF- β has been shown to play an important role in the development of radiation-induced pneumofibrosis in various animal models (see Section 2.7.3). Several clinical studies have also shown that persistently elevated plasma TGF- β at the end of a course of radiotherapy for lung cancer is a risk factor for radiation pneumonitis (Anscher et al., 1998; Fu et al., 2001). However, other studies failed to confirm TGF- β levels as a general and independent predictor of lung damage (De Jaeger et al., 2004; Evans et al., 2006). A multivariate analysis of the data reported by De Jaeger et al. showed that mean lung dose was significantly correlated with the plasma TGF- β level, and that this was the most important prognostic factor for development of pneumonitis. In a recent review of biological markers to predict the risk of radiation-induced lung injury, the authors concluded that there was currently no reliable and validated predictive test that could be used for treatment decisions (Fleckenstein et al., 2007a). Although TGF- β may have the potential to fulfil the requirements of a predictive assay, they concluded that more prospective studies with adequate patient numbers were required to establish its true value.

2.7.3. Experimental data and mechanisms of damage

(338) One of the earliest changes in irradiated lung tissue is an increased level of alveolar surfactant, which can be seen within hours of irradiation and is probably a direct effect of radiation on type II pneumocytes (Rubin et al., 1980). Increased alveolar surfactant may persist for 2–6 weeks, but resolves before the onset of pneumonitis. Another early event (days to weeks after irradiation) is damage to the capillary endothelium, with associated changes in vascular permeability leading to exudation of plasma proteins into the alveolar spaces. Changes in lung perfusion and oxidative stress have also been identified within 1 week of irradiation. These changes all take place before the loss of type I pneumocytes and denuded epithelium occurs. Focal denudation of endothelial cells may also occur, with occlusion of capillaries by debris and thrombi at sites where the basement membrane is exposed (Phillips and Margolis, 1972; Gross, 1980; Fleckenstein et al., 2007b).

(339) Damaged endothelial cells and type II pneumocytes, as well as activated macrophages, also produce increased levels of various inflammatory mediators that induce interstitial inflammation and alveolar collapse (Arpin et al., 2005; Chen et al., 2005). Experimental studies have shown that these changes are radiation dose dependent (Rubin et al., 1992) and often biphasic. The initial response in mouse lung occurs within hours of irradiation, followed by a second, more persistent expression of inflammatory cytokines that coincides with the onset of pneumonitis (Rube et al., 2004). The inflammatory response in irradiated lung is characterised by accumulation of protein-rich exudates, with abundant mast cells and lymphocytes. The

alveolar space becomes filled with fibrin, debris, and an increasing number of macrophages and other inflammatory cells (Travis, 1980; Lehnert et al., 1991). These recruited inflammatory cells also produce ROS and profibrotic cytokines, thus perpetuating the damage. The inflammatory changes are not necessarily restricted to the irradiated part of the lung. Generalised hypersensitivity may occur as the result of concomitant infection or immunologically mediated phenomena (Morgan and Breit, 1995). The early phase of radiation injury in the lung is therefore due to a combination of cell loss (type I pneumocytes and endothelial cells), increased microvascular permeability, and increased production of inflammatory cytokines. The functional consequences of this are a dose-dependent increase in the rate of breathing (Travis et al., 1979) and lethality after single doses of >11 Gy (Travis and Tucker, 1986).

(340) The late phase of radiation injury in the lung is characterised by progressive vascular sclerosis and fibrosis of alveolar septa. The alveoli later collapse and are replaced by connective tissue. Impaired pulmonary blood flow with a loss of capillary perfusion has also been demonstrated in areas of irradiated lung free of obvious fibrosis (Sharplin and Franko, 1989). There is experimental evidence that susceptibility to radiation-induced pulmonary fibrosis is a heritable trait, controlled by at least two autosomal genes that function independently (Franko et al., 1996; Haston and Travis, 1997). Although the interstitial fibrosis is, to some extent, a reaction to parenchymal cell loss, various cytokine-mediated multicellular interactions between the pneumocytes, endothelial cells, fibroblasts, and macrophages are involved in both initiation and maintenance of the fibrotic response (Rubin et al., 1992; McDonald et al., 1995; Morgan and Breit, 1995; Wall and Schnapp, 2006).

(341) TGF- β , in particular, plays a key role in the development of pneumofibrosis via accelerated terminal differentiation of progenitor fibroblasts to fibrocytes (Finkelstein et al., 1994; Burger et al., 1998; Hill, 2005). Experimental models of thoracic irradiation have demonstrated dose-related increased expression of TGF- β preceding lung fibrosis (Finkelstein et al., 1994; Rube et al., 2000). Radiation-induced increases in TGF- β production were also shown to be greater in fibrosis-prone strains of mice than resistant strains (Johnston et al., 1995). Further evidence for the involvement of TGF- β comes from studies showing that inhibition of TGF- β signalling inhibited radiation-induced activation of TGF- β in irradiated lungs, and decreased both the inflammatory and fibrotic response to radiation (Rabbani et al., 2003; Anscher et al., 2006, 2008). The late phase of radiation injury in the lung is therefore due to a combination of developing fibrosis and loss of capillary function, with associated non-perfusion of lung parenchyma.

(342) The early and late phases of lung damage can be clearly dissociated (Travis, 1980). Although a severe pneumonitis phase is often followed by fibrosis, late fibrosis may develop in the absence of previous pneumonitis, and it occurs at lower doses. This was shown in experimental studies where split-dose thoracic irradiation was given to mice over a period of several weeks. These studies demonstrated significant sparing of the acute pneumonitis phase (Travis and Down, 1981), and a remarkable tolerance to re-irradiation at 2–6 months after subtolerance initial irradiation (Terry et al., 1988), although many of the animals subsequently died with late lung injury.

The sparing of acute damage with increased overall treatment time is probably due to the stimulated proliferation of type II pneumocytes, offsetting the epithelial cell loss in irradiated lungs and thereby limiting the acute response. Quantitative evaluation of human lung data also indicates a substantial time factor of approximately 0.5 Gy/day for acute pneumonitis, whereas no time factor has been demonstrated for late fibrosis (Bentzen et al., 2000).

(343) Fractionation studies in experimental animals show that the lung has a large capacity for repair of sublethal damage, and that tolerance is strongly influenced by the size of the dose per fraction. Experimental data from rodents, pigs, and dogs are generally well described by an LQ model and give α/β ratios of 2–4 Gy (Herrmann et al., 1986; Parkins and Fowler, 1986; McChesney et al., 1989; Vegesna et al., 1989). In studies where both acute pneumonitis and late fibrosis endpoints were studied, the α/β ratios tended to be slightly lower for fibrosis. Estimates of repair half-time in lung, based on incidence of pneumonitis, are generally in the range of 0.7–1.2 h (Travis et al., 1987; Parkins et al., 1988; Vegesna et al., 1989; Van Rongen et al., 1990a,b). Some studies have identified two components of repair: a fast component with a half-life of 0.4 h (dominating the effect), and a slow component with a half-life of 4 h (Van Rongen et al., 1993).

2.7.4. Non-therapeutic exposures

(344) Analysis of data from the Japanese atomic bomb survivors demonstrates a significant increase in the lifetime risk of respiratory disease mortality. Risk estimates were in the range of 18% per Sv for doses of 0.5–2.5 Sv (Preston et al., 2003). More limited data from the Chernobyl nuclear reactor accident also give some evidence for development of fatal interstitial pneumonitis in individuals who received BMT after exposure to doses of 5.6–13.4 Gy (Baranov et al., 1989). Additional reports indicate a high incidence of pulmonary infectious complications in postmortem lung specimens of Chernobyl accident victims (Vlasov and Kvacheva, 1996). At least some of these cases were probably due to opportunistic infections resulting from bone marrow suppression, rather than direct damage to the lung tissue.

Internal exposures

(345) The best-explored form of radiation pneumofibrosis associated with internal exposure is plutonium pneumofibrosis (PP), which has been demonstrated in clinical studies on plutonium workers after exposure to ^{239}Pu (Khokhryakov et al., 1996; Okladnikova et al., 2002; Newman et al., 2005) and in experiments on animals (Koshurnikova et al., 1972; Muggenburg et al., 1988; Brooks et al., 1992). Studies conducted in Rocky Flats have shown an increased risk of pneumofibrosis at lung doses of >10 Sv (Newman et al., 2005). Higher doses were associated with earlier development and greater severity of PP. Latent periods for symptomatic PP were usually in the range of 7–17 years, but individual cases were evident 3–5 years after first exposure to plutonium aerosol. Biochemical and histological signs of fibrosis appear as early as 2 months after exposure.

(346) A typical feature of PP is the occurrence of fibrosis predominantly in the upper parts of the lungs (Okladnikova and Guskovava, 2001). In cases of inhalation of radionuclides, their distribution in different parts of the respiratory tract is dependent on the size of the particles and their solubility. Particles penetrating into the lungs can be absorbed by macrophages capable of migration, or by type II pneumocytes. Soluble radionuclides can pass through the alveolar wall into the bloodstream. Retention of inhaled radionuclides in the lung depends on the chemical form of the compound (Dagle and Sanders, 1984). Inhaled plutonium, especially insoluble oxides, is retained for many years after irradiation. Plutonium particles are usually deposited in the terminal bronchioles, peribronchial alveolar septa, and subpleural lymphatic vessels. 'Hot spots' in a small lung volume are exposed to much higher doses than those estimated for the whole lung, and are sufficient to cause local cell loss (Hahn et al., 2004).

(347) Macrophages that have absorbed radionuclides such as ^{239}Pu play a leading role in the development of PP. Changes during the early stage of PP include infiltration of foci of fibrosis by mononuclear cells surrounding the alveoli, alveolar ducts, and bronchioles; increased numbers of type II alveolar epithelial cells; and accumulation of exudates. Later on, accumulations of histiocytes absorbing exudative effusion can be observed. There is a significant thickening of the alveolar septa due to oedema; formation of connective tissue; and accumulation of mast, plasmatic, and alveolar cells. Outgrowth of connective tissue around the alveoli represents the morphological basis of PP. The most common cause of death in cases of pneumofibrosis is progressive pulmonary cardiac insufficiency (Guskova, 2004; Wall and Schnapp, 2006).

2.7.5. Summary

(348) Symptomatic lung toxicity is common in patients irradiated for cancer of the lung, breast, and oesophagus, and mediastinal lymphoma. The early pneumonitis phase of damage is due to a combination of epithelial cell loss, microvascular permeability, and increased expression of inflammatory cytokines. Late lung damage is characterised by progressive vascular sclerosis and interstitial fibrosis. The fibrosis occurs partly as a response to parenchymal cell loss but persistent overexpression of fibrotic cytokines, especially TGF- β , actively contributes to this process. The most important factors determining risk of radiation pneumonitis and fibrosis are total exposure dose and volume of irradiated lung. Other factors, such as genetic predisposition, comorbidity, and additional chemotherapy, may modify these risks.

2.8. Urinary tract

2.8.1. Anatomical features and proliferative organisation

(349) The urinary system comprises the kidneys, ureters, bladder, and urethra. It is responsible for water and electrolyte balance, and for excretion of toxic metabolic

waste products. The kidneys also produce renin, involved in homeostatic maintenance of blood pressure, and erythropoietin, which stimulates red blood cell production in the bone marrow.

Kidneys

(350) The kidneys are paired organs with their basic FSUs, the nephrons, arranged in a parallel fashion. Each human kidney contains over a million nephrons, consisting of a glomerulus, with its capillary network for filtration of the blood, and a long tubular segment (up to 55 mm long in man). The long tubular segment is divided into a proximal convoluted section, responsible for the majority of water and ion resorption from the glomerular filtrate; the loop of Henle, which generates a high osmotic pressure in the extracellular fluid of the renal medulla; and the distal convoluted tubule, for resorption of sodium ions. The nephrons drain into a system of collecting ducts, which, in turn, drain the processed urine into the ureters. The glomeruli and convoluted tubules are located in the cortical region of the kidney, with the collecting tubules and part of the loops of Henle in the medulla. The tightly coiled capillaries of the glomeruli are in close association with epithelial podocytes and mesangial cells, and are surrounded by the Bowman's capsule. The epithelium of the Bowman's capsule is continuous with that of the single-layered epithelium lining the renal tubule. A fine balance between glomerular filtration and tubular resorption is maintained via the juxtaglomerular apparatus, which secretes renin and regulates both blood pressure and plasma volume. This balance is maintained in the face of injury, until a critical level of disruption is reached and the affected nephron shuts down. The parallel arrangement of the nephrons confers a considerable degree of redundancy in the kidney, and allows remaining undamaged nephrons to maintain normal renal function unless the number of affected nephrons becomes too great.

(351) The adult kidney is a slow turnover tissue, with low levels of proliferation in both tubular cells and glomeruli (labelling index <0.5%). However, the kidney is capable of responding to surgical or chemical injury by transient increased proliferation lasting <1 month after injury. Irradiation also induces an early, dose-related increase in proliferation in both proximal tubules (Otsuka and Meistrich, 1990) and glomeruli (Robbins et al., 1994). Stimulated proliferation after irradiation has been shown to precede the onset of functional damage and to persist for 6–12 months (i.e. during the period of progressive renal failure). Proliferation in the kidney therefore does not seem to aid recovery from radiation injury. Unilateral nephrectomy given after irradiation also precipitates latent renal injury rather than stimulating recovery (Otsuka and Meistrich, 1992).

Bladder

(352) The mammalian bladder is a hollow, muscular organ that collects urine produced by the kidneys, and stores it until voluntary micturition via the urethra. The bladder consists of a mucosa with three to five layers of transitional epithelium, fibrous connective tissue containing the blood vessels and nerve fibres, and three

smooth muscle layers. Three sphincters are associated with the muscle layers, and these maintain continence and allow accumulation of urine beyond the point at which the bladder would reflexly void. Striated muscles of the pelvic floor also contribute to control of voiding.

(353) The urothelium is a polyploid tissue in which the DNA content increases from the basal cells (2n) to surface cells (polyploid). Superficial urothelial cells, sometimes called ‘umbrella cells’, are very large, covering up to 20 underlying epithelial cells when the bladder is distended. They have a highly specialised luminal surface membrane, which confers both the ability to expand and to restrict passage of water and small ions between the blood and urine. The luminal surface of this plasma membrane comprises hexagonal plaques, separated by thinner ‘hinge’ areas, allowing folding and invagination of the membrane as the bladder contracts. The plaque areas contain four integral membrane proteins called ‘uroplakins’ (UPs), and UP-III has been shown to have an important role in maintaining the impermeability of the urothelium (Hu et al., 2002). A glycosaminoglycan layer also covers the luminal surface of the urothelium, which, together with tight junctions between adjacent superficial cells, further restricts permeability (Hicks, 1975; Parsons et al., 1990).

(354) Under normal conditions, the urothelium has an extremely slow cell turnover time of >100 days. However, it is capable of rapid turnover in response to infection, surgical or chemical stimulation, or after irradiation. Mechanical or chemical trauma induces rapid proliferation within a few days. This is usually initiated in the basal layer, although cells of all ploidy levels are capable of division. In contrast, stimulated proliferation of irradiated rodent bladder does not begin until approximately 3 months, coinciding with the onset of radiation-induced cell loss and denudation, and does not reach a maximum (cell turnover <6 days) until 6–9 months (Stewart, 1986; Stewart and Williams, 1991). Studies of Stewart et al. showed that mouse bladder remains in a state of stimulated, rapid proliferation for up to 19 months after high single-dose irradiation, resulting in a hyperplastic but disorganised urothelium without replacement of properly differentiated, polyploid superficial cells (Stewart et al., 1980; Stewart, 1985).

2.8.2. Clinical data on therapeutic doses

Kidneys

(355) The kidneys are the most sensitive organs of the urinary tract. The low radiation tolerance and late onset of injury of the kidney has been recognised since the 1950s (Kunkler et al., 1952; Luxton, 1961). Detailed analyses of patients given abdominal irradiation for seminoma of the testes established that exposure of the whole of both kidneys to 23 Gy, in approximately 1-Gy fractions over 5 weeks, resulted in significant risk of renal damage. This was categorised as: acute radiation nephritis (latency 6–12 months), chronic radiation nephritis (1.5–4 years), benign hypertension (1.5–5 years), late malignant hypertension (1.5–11 years), and proteinuria (5–19 years). The late onset of radiation nephropathy was emphasised in a

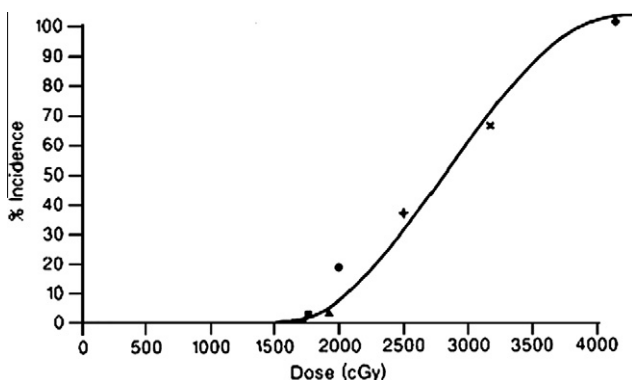


Fig. 2.11. Dose response for symptomatic kidney injury after bilateral kidney irradiation. Reproduced from Dawson et al. (2010). For full references of data used, see original Fig. 2 in Dawson et al., 2010.

review of 84 patients who received abdominal doses of approximately 20 Gy for treatment of peptic ulcer (Thompson et al., 1971). Renal disease developed in 31 of these patients (37%) after latent periods of 1–14 years. The latent period in over half of the patients who developed renal damage was >10 years. This illustrates the need for a long follow-up time when evaluating tolerance doses for the kidney. A recent review of clinical data for local exposure of the whole of both kidneys is consistent with 5% incidence of injury at 5 years after 18–23 Gy in doses per fraction <1.25 Gy, and 50% risk of injury after 28 Gy (Dawson et al., 2010) (Fig. 2.11).

(356) Clinical symptoms of acute radiation nephritis include oedema, dyspnoea, headache, vomiting, and hypertension. Normocytic anaemia may also develop. Symptoms of chronic radiation nephritis are albuminuria, hypertension, and reduced renal function (increased blood urea nitrogen and serum creatinine, decreased renal plasma flow). Patients with proteinuria may have apparently normal renal function, although their reserve renal function is impaired and renal failure may occur after stress. Benign hypertension is usually accompanied by proteinuria, and may lead to cardiovascular problems if not treated (Stewart and Williams, 1991; Cassady, 1995). Hypertension after renal irradiation is the result of increased production of angiotensin II, but it is not clear whether this is mediated by increased secretion of renin, due to radiation-induced vascular damage and ischaemia, or whether this occurs independent of circulating renin levels.

(357) Tolerance doses for impaired renal function after partial volume exposures are considerably higher than for whole-organ exposure due to compensatory increased function and hypertrophy in the contralateral unirradiated or low-dose kidney. This compensatory effect can maintain a near-normal total renal function, despite significant damage in the heavily irradiated kidney. Non-invasive renography and external scintigraphic scanning techniques have been used to monitor progressive deterioration of both tubular and glomerular renal function in irradiated

kidneys. The incidence of reduced renal activity in the irradiated kidney is both dose and volume dependent, with an estimated ED₅₀ of <10 Gy (fractionated) for 100% volume irradiated, increasing to 18.5 Gy for 20% volume irradiated (Kost et al., 2002). Prospective, sequential imaging of patients with abdominal tumours showed that loss of function in the heavily irradiated kidney (>22 Gy as fractionated dose) progressed at a rate of approximately 1–2% per month relative to the contralateral kidney (12–13 Gy), decreasing to 60% of pretreatment values at 3 years and 25% at 6–9 years (Dewit et al., 1990, 1993; Kost et al., 2002). Selective angiography and captopril renography revealed both structural and functional vascular defects in patients with radiation-induced renal insufficiency, leading to renovascular hypertension in approximately one-third of cases (Verheij et al., 1994). A recent review (Dawson et al., 2010) suggested that the clinical data are consistent with a moderate risk of renal toxicity for fractionated total doses of 20 Gy to >50% kidney volume, and 26 Gy for 30–40% volume. However, it was pointed out that these estimates were associated with substantial uncertainty.

(358) TBI combined with BMT was commonly used in the 1980s and 1990s for treatment of various haematopoietic cancers, although this is less commonly used today. Single doses of 7.5–10 Gy or total doses of 12–14 Gy in 2-Gy fractions were associated with a significant risk of compromised renal function (Tarbell et al., 1988; Lawton et al., 1991, 1992; Lonnerholm et al., 1991; Rabinowe et al., 1991). The onset of nephropathy after TBI is generally shorter (<1 year) than after abdominal irradiation. In addition to typical symptoms of radiation nephropathy, haemolytic uraemic syndrome is often seen, implicating the glomeruli as the principal site of damage. These patients usually receive pretransplant conditioning with chemotherapy and immunosuppressive drugs, which significantly increases the risk of renal injury (Cheng et al., 2008). However, the damage is clearly related to radiation dose, and the actual incidence of nephropathy after BMT/TBI can be reduced from 26% to 6% at 18 months by introducing renal shielding to reduce the renal dose from 14 Gy to 12 Gy in seven fractions (Lawton et al., 1991, 1992).

Bladder and ureters

(359) The bladder and lower ureter receive high doses of radiation during treatment of cancer of the bladder, prostate, and cervix. The tolerance of the bladder is appreciably higher than that of the kidney, with a complication risk of approximately 5% for total doses of 55–60 Gy given as 2-Gy fractions over 5–6 weeks. Total doses of up to 65 Gy in 2-Gy fractions can be delivered to bladder volumes of <50% without increasing the risk of damage (Rubin and Casarett, 1972; UNSCEAR, 1982; Marks et al., 1995; Viswanathan et al., 2010). However, the risk of injury may increase considerably for whole-bladder irradiation with larger doses per fraction (Lindholt and Hansen, 1986) or two fractions per day (Lievens et al., 1996; Moonen et al., 1997).

(360) The damage resulting from larger doses, or shorter overall treatment time, includes inflammatory cystitis, ulceration, fistula, fibrosis, contraction, and urinary obstruction. Two waves of injury are seen: an acute, transient

response that occurs towards the end of a fractionated course of therapy and resolves within a few weeks; and a non-reversible phase of damage that may occur progressively from approximately 6 months after treatment. Symptoms of the acute phase of damage include frequency, urgency, and dysuria. The underlying cause of these symptoms is inflammation (hyperaemia and oedema), sometimes complicated by bacterial infection, which is treatable with antibiotics (Stewart and Williams, 1991).

(361) Late progressive bladder damage is due to a combination of urothelial cell denudation, the formation of ulcers and necrosis, submucosal telangiectasia, and developing fibrosis, which is probably secondary to late vascular damage and ischaemia. The formation of calcareous deposits may also occur. These changes are normally seen within 2–3 years of irradiation and can result in permanent reduction of bladder capacity, in some cases requiring total cystectomy.

(362) The ureters are more resistant than the bladder, and considerably more resistant than the small bowel which is in close proximity. The incidence of uterine obstruction after doses of 60–70 Gy (in 2-Gy fractions, without previous transurethral resection) is <5% (Marks et al., 1995). The relative resistance of the ureters to development of stenosis was also confirmed in experimental studies in dogs and rats (Knowles and Trott, 1987; Kinsella et al., 1988; Gillette et al., 1989). However, urothelial biopsies taken from Ukrainians living for >15 years in caesium-contaminated areas after the Chernobyl accident did reveal a very high incidence of chronic proliferative cystitis: 89% compared with an incidence of 19% in a group of people from non-contaminated areas of Ukraine (Romanenko et al., 2002). The exposed population also had very high levels of DNA repair enzymes (base and nucleotide excision repair) in their urothelial biopsies. This was consistent with the induction of oxidative stress and activation of repair enzymes by long-term exposure to radiation.

2.8.3. Experimental data and mechanisms of damage

Kidneys

(363) Experimental studies demonstrate progressive, dose-dependent decreases in renal function after local irradiation of one or both kidneys. The time of onset of damage is inversely related to dose, but life-threatening decreases in renal function are not normally seen earlier than 4–6 months after irradiation in rodents, even after single doses of >12 Gy, although this can occur earlier in dogs and pigs (Hoopes et al., 1985; Robbins et al., 1989). Significant decreases in glomerular filtration rate and renal plasma flow (Robbins and Bonsib, 1995), and increased production of low-osmolality urine (Williams and Denekamp, 1983; Stevens et al., 1991) do, however, occur within 3 months of renal irradiation. Dose-related development of anaemia, hypertension, increased blood urea nitrogen, and proteinuria tend to occur at slightly later times (Alpen and Stewart, 1984; Moulder et al., 2004).

(364) Doses associated with severe functional impairment at >9 months after irradiation are in the range of a single dose of 7–9 Gy. This is consistent with a histological analysis of renal damage in rhesus monkeys at 6–8 years after TBI doses of 4.5–8.5 Gy. Mild-to-moderate increased mesangial matrix and capillary dilatation were seen in glomeruli, together with mild tubular atrophy and fibrosis, at doses of 7–8 Gy, but not after lower doses (Van Kleef et al., 2000). Renal tolerance in young animals (and in children) is generally similar to the adult. However, the threshold for renal damage in immature developing kidneys is much lower, as shown in studies exposing newborn beagle pups to TBI doses of only 2.2–3.6 Gy (Jaenke and Angleton, 1990).

(365) The development of renal functional damage appears to be relentlessly progressive, even after low doses of radiation. This is despite the proliferative regeneration that occurs in both glomerular and tubular cells from 1 to 3 months after irradiation, and the regeneration of whole tubules that has been seen at 15 months (Withers et al., 1986; Otsuka and Meistrich, 1990; Robbins et al., 1994). The lack of functional recovery in the kidney is especially apparent in experimental systems where kidneys were re-irradiated after low initial doses that were insufficient to lead to renal impairment in <1 year (Stewart et al., 1988, 1989, 1994; Stewart and Oussoren, 1990; Robbins et al., 1991). Such studies showed that there is little or no long-term recovery and that re-irradiation seems to ‘unmask’ occult damage from the initial low dose of radiation, causing rapid and severe onset of renal damage after the re-irradiation. This implies that either the proliferative regeneration that occurs is insufficient to compensate for the rate of cell loss after renal irradiation, or that the surviving, but damaged, cells are incapable of proper organisation and function.

(366) The pathogenesis of radiation nephropathy has long been debated, with some authors favouring the tubules as the initial site of injury and others favouring endothelial cells of the glomeruli or larger vessels as the critical lesion. To a large extent, these differences in opinion can be attributed to the different doses and follow-up times used in the investigations. Detailed morphogenic studies have identified early damage (2–4 weeks after high doses, 15 Gy) in the proximal tubular cells, which progresses to focal areas of tubular cell loss, initially clustered around the arcuate arteries and veins, and progressing to more widespread tubular necrosis with interstitial fibrosis (Michalowski, 1986). However, such early tubular cell damage has not been reported after radiation doses of <12 Gy. The earliest morphological changes seen in irradiated pig kidneys after low doses (3–6 weeks after 9.8 Gy) are swelling and activation of glomerular capillary endothelial cells, followed by leukocyte attachment (Jaenke et al., 1993; Robbins et al., 1993). These early changes are followed by increased capillary permeability and exudation of plasma and red blood cell components, as well as increased production of inflammatory and thrombotic mediators by the activated endothelial cells (Weshler et al., 1988; Robbins and Bon-sib, 1995; Stewart et al., 2001). Prominent features at later times are thickening of glomerular capillary loops, telangiectatic capillaries, mesangiolysis, glomerular thrombosis, and glomerular sclerosis. Thrombotic lesions occur in both arterioles and larger arteries, and non-thrombotic intimal occlusive lesions also occur in large

arteries. Tubular changes during this period include thickening of the basement membrane, cellular atrophy followed by necrosis, and interstitial fibrosis (Stewart and Williams, 1991; Robbins and Bonsib, 1995).

(367) Fractionation studies show that the kidney has a large capacity for repair of sublethal damage, and that the tolerance is strongly influenced by the size of the dose per fraction. Experimental data are generally well described by an LQ model, and α/β ratios of 2–3 Gy fit most of the experimental data for doses per fraction of 2–10 Gy (Stewart and Williams, 1991; Joiner et al., 1992). Estimates of repair half-times are of the order of 1.3–2 h (Van Rongen et al., 1990a; Joiner et al., 1993). Deviations from the LQ model have been shown for doses per fraction of <1–2 Gy using more than one fraction per day (Stewart et al., 1987b). This deviation can partly be explained by incomplete repair during short interfraction intervals of <6 h, although reduced induction of molecular repair mechanisms at low doses per fraction may also contribute (Joiner and Johns, 1988).

(368) Cisplatinum is sometimes given in combination with abdominal irradiation (e.g. for cervical and testicular cancers). Increased renal toxicity is a concern here as cisplatinum is known to cause degeneration and necrosis of proximal convoluted tubules. Renal toxicity occurs within 1 week of cisplatinum administration, but usually resolves within 1–3 months unless very high doses have been given. Cisplatinum, given before or after irradiation, also significantly increases late renal toxicity, particularly when the drug is given after irradiation (Stewart et al., 1987a; Moulder and Fish, 1991; Van Rongen et al., 1994). This may partly be explained by reduced drug clearance in animals with developing radiation damage (Moulder et al., 1986), but drug-induced cell killing is also likely to precipitate subclinical radiation injury. Whatever the mechanism, cisplatinum given several months after renal irradiation with a low-to-moderate dose was found to be much more toxic than the reverse sequence.

Bladder

(369) Experimental studies in mice identified an acute, transient functional response, that occurs within the first month after irradiation, and a non-reversible phase of damage that develops progressively from approximately 4 to 6 months, depending on dose.

(370) During the acute phase, reduced bladder capacity and increased urination frequency are seen, with ED₁ of >10 Gy and ED₅₀ of approximately 20 Gy (Stewart and Williams, 1991; Dorr and Schultz-Hector, 1992; Dorr and Beck-Bornholdt, 1999). This early damage is not associated with marked necrosis or loss of urothelium (Stewart, 1986; Dorr et al., 1998), although oedematous cytoplasm and lysosomes in both urothelial cells and microvascular cells can be seen using electron microscopy (Antonakopoulos et al., 1984). A reduction in the number of large superficial cells has also been shown during the early period after irradiation (Jaal and Dorr, 2006a).

(371) The highly specialised, polyploid, superficial urothelial cells normally form an impermeable barrier preventing transfer of ions across the bladder. Mechanical

trauma or chemical carcinogens damage the luminal membranes of these cells and permeability increases (Hicks, 1975); this exposes the bladder wall to chemical irritation from urine components. Radiation similarly induces early changes in expression levels of various proteins, including progressive loss of UP-III, in the urothelial cell membranes, which impairs the barrier function of the urothelium during the first month after irradiation (Dorr et al., 1998; Jaal and Dorr, 2006b). Transient, early changes in cyclo-oxygenase-2 expression and prostaglandin metabolism in endothelial cells are also induced after bladder irradiation, which results in vasodilatation, increased muscle tone, and decreased bladder capacity (Jaal and Dorr, 2006b,c). Increased expression of intercellular adhesion molecule 1 (ICAM-1) in the microvascular endothelial cells is involved in triggering the early, inflammatory response (Jaal and Dorr, 2005).

(372) From 3 to 6 months after irradiation of mouse bladder, urothelial cell denudation is seen with increased proliferative activity in the remaining epithelial and endothelial cells, leading to multifocal atypical hyperplasia. The superficial cells lose their characteristic luminal membranes, becoming small and immature. Hyperplasia of endothelial cells and increased leakage of the microvasculature in the submucosa is also seen, along with perivascular fibrosis and degeneration of muscle layers with increased TGF- β immunoreactivity and collagen deposition (Stewart, 1986; Kraft et al., 1996; Jaal and Dorr, 2006c). Bladder calculi developed in mouse bladder from 1 year after irradiation (Stewart, 1986) and, in rats, radiation-induced urothelial tumours developed from 20 months after irradiation (Antonakopoulos et al., 1982). The combination of severe urothelial changes and developing fibrosis in the submucosa and muscle layers results in persistent increased urination frequency and reduced bladder capacity (Stewart et al., 1978, 1991; Lundbeck et al., 1993).

(373) Fractionation studies in mice show considerable sparing of late damage with increasing number of fractions, with total doses of approximately 70 Gy in 20 fractions giving equivalent damage to a single dose of 25vGy. LQ analysis of fractionated dose data for late functional damage after bladder irradiation gave α/β ratios of 4–7 Gy, which are slightly higher than for most other slowly dividing tissues (Stewart et al., 1981, 1984; Dorr and Bentzen, 1999). LQ analysis of fractionated dose data for acute functional damage after bladder irradiation gave α/β ratios of 11–12 Gy, consistent with other acute responding epithelial tissues, despite the fact that urothelial cell depletion did not seem to be the cause of the early response (Dorr and Schultz-Hector, 1992).

(374) Pelvic irradiation is sometimes given in combination with drugs such as cyclophosphamide (ovarian cancer, rhabdomyosarcomas of urogenitary tract) or cisplatinum (bladder cancer, cervical cancer, ovarian cancer). Cyclophosphamide is specifically toxic to the bladder, since direct contact of its metabolites with the urothelium causes epithelial denudation and haemorrhage. This is followed by rapid proliferation in the remaining urothelial cells (Stewart, 1985). Experimental studies in which cyclophosphamide was given before or after irradiation of the mouse bladder showed increased damage (urinary frequency, haematuria, and reduced bladder volume) within 1 month after irradiation. Part of this effect is

probably due to stimulated urothelial proliferation after cyclophosphamide and precipitation of latent radiation injury. Increased late damage was also seen for combined irradiation and cyclophosphamide, although this seems to be largely due to additive toxicity from the two agents rather than increased radiosensitivity (Edrees et al., 1988; Lundbeck et al., 1993). Cisplatin is not specifically toxic to the bladder when used alone, but does significantly increase both early and late radiation damage (Lundbeck and Overgaard, 1992; Lundbeck et al., 1993).

(375) Superficial bladder carcinomas are often treated with a combination of transurethral resection and intravesical chemotherapy. Patients who subsequently develop recurrence are given either cystectomy or radiotherapy. An experimental study in mice showed that repeated intravesical mitomycin C or doxorubicin caused acute, transient bladder damage (increased frequency and reduced volume capacity), but chemotherapy did not increase the sensitivity to subsequent irradiation (Post et al., 1995).

2.8.4. Summary

(376) Renal damage is dose limiting for abdominal irradiation including both kidneys. The onset of renal damage is late (>10 years after low doses) and progressive. This emphasises the need for long-term follow-up to assess tolerance. Shielding (part of) one kidney leads to a considerable increase in tolerance due to compensatory function in the contralateral kidney. Previously irradiated kidneys are at increased risk of damage from subsequent nephrotoxic agents (e.g. chemotherapy).

(377) Radiation tolerance of the bladder is considerably higher than that of the kidney. However, substantial numbers of patients treated with high-dose radiotherapy for prostate cancer, cervical cancer, or bladder cancer develop toxicity. Transient increases in urination frequency occur towards the end of treatment due to inflammation and oedema in the bladder mucosa. This may be followed by telangiectasia and erosion of the bladder mucosa, and progressive fibrosis of the bladder wall from approximately 6 to 12 months, resulting in permanent reduction in bladder capacity.

2.9. Musculoskeletal system

2.9.1. Anatomical features

(378) Bone represents the structural framework of the body and provides attachments for skeletal muscles and protection for the brain, thoracic, and pelvic organs. Bones also provide room for haematopoiesis and serve to collect, store, and release calcium and other ions. Hence, bone contains 99% of the body's calcium and a large part of its phosphate. By weight, 60% of the bone mass is calcium, while collagen comprises 30%.

(379) Bone matrix contains osteoprogenitor cells, osteoblasts, osteocytes, and osteoclasts, as well as a rather rich network of blood vessels. The vessels supply the bone marrow sinuses where haematopoiesis occurs.

(380) Bone is made either by intramembranous or endochondral formation. Intramembranous formation – as seen, for example, in small bones, vertebral bodies, and the skull – occurs by maturation of osteoprogenitor cells into osteoblasts that cause deposition of mineralised bone matrix. In contrast, endochondral bone formation takes place at cartilaginous epiphyseal plates, so-called ‘growth plates’. Here, cartilage cells organise into columns which are then invaded by osteoblasts that deposit collagen and hydroxyapatite along the cartilage matrix.

(381) The healing of bone fractures involves removal of dead cells and other matter, followed by deposition of osteoid material around the fragments, the so-called ‘callus’.

(382) The individual fibres of skeletal muscle are a syncytium of actin and myosin filaments and multiple nuclei arranged around the periphery of the cell, enclosed in a thin connective sheath (the endomysium). Muscle bundles are formed by several muscle fibres enclosed in a perimysium, while the muscle itself consists of several bundles in an epimysium.

2.9.2. Clinical data on therapeutic doses

(383) Four types of non-neoplastic complications of clinical importance occur after radiation exposure of bone: radio-osteonecrosis, stress fractures, impaired fracture healing, and abnormal bone growth in children. The radiation tolerance of bone in a given situation depends on the age of the subjects; inclusion of bone growth zones in the radiation field (and on the specific growth zones included); and the presence of other tissue pathology, such as decaying teeth, infection, or tumours.

(384) Mature bone is relatively radioresistant (Parker, 1972). Radiation doses up to 65 Gy (in 2-Gy fractions), even over joint spaces, are generally not associated with significant morbidity. The most important determinant of complication risk appears to be the volume treated with doses of >55 Gy (Karasek et al., 1992).

(385) Radio-osteonecrosis is a clinically important complication of bone irradiation. The clinical presentation of radio-osteonecrosis usually occurs >1–2 years after treatment. It is most commonly seen in the mandible or temporal bone after treatment of head and neck neoplasms, and in the pelvis, sacrum, or femoral head after treatment of pelvic tumours. Radio-osteonecrosis occurs in 2–20% of patients when fractionated radiation doses of >60–65 Gy are used (Cooper et al., 1995; Fajardo et al., 2001). Emami et al. (1991) estimated total fractionated doses for 5% and 50% necrosis of the femoral head at 5 years to be 52 Gy (ED_{5/5}) and 65 Gy (ED_{50/5}). For impaired function of the temporomandibular joint, the equivalent estimated doses are 60 Gy (ED_{5/5}) and 72 Gy (ED_{50/5}).

(386) Spontaneous stress fractures are a clinically important complication of bone irradiation. After therapeutic radiation doses, radiological evidence of (subclinical)

stress fractures are common. While many stress fractures are asymptomatic, such fractures may be associated with pain and increased susceptibility to trauma leading to overt fractures (Blomlie et al., 1996). When overt fractures do occur, they heal slowly or fail to heal altogether. Patients with connective tissue disorders appear to be particularly predisposed to radiation-induced stress fractures (Bliss et al., 1996). The estimated total tolerance doses (2-Gy fractions) for pathological rib fractures after chest wall irradiation are 50 Gy ($ED_{5/5}$) and 65 Gy ($ED_{50/5}$), respectively (Emami et al., 1991). The α/β ratio for spontaneous rib fractures after radiation therapy for breast cancer has been estimated to be in the range of 1.8–2.8 (Overgaard, 1988; Hopewell, 2003).

(387) In contrast to mature bone, growing bone is much more radiosensitive (Tefft, 1972). Clinical manifestations after radiation therapy in children include stunted or asymmetric growth, scoliosis, facial deformities, and micrognathia (Sonis et al., 1990). The changes are more severe in young children, especially below the age of 2 years. Clinical observations suggest a total fractionated $ED_{5/5}$ dose for growing bone in children in the range of 15–30 Gy, with 25 Gy often suggested as a critical threshold (Fajardo et al., 2001). Consistent with the clinical observations, studies in atomic bomb survivors from Hiroshima and Nagasaki also show significant age-dependent growth retardation in individuals of both sexes who were <19 years of age at the time of bombing (Nakashima et al., 2002).

(388) Irradiation of the skeletal musculature occurs in the clinical setting during diagnostic procedures, during the radiotherapeutic management of cancer, and during prevention of heterotopic bone formation in patients receiving joint replacements. Mature muscle is relatively resistant to radiation, but less so than previously assumed. The radiation response of skeletal muscle exhibits a prominent volume effect (i.e. injury becomes clinically manifest mainly after irradiation of large muscle groups). Complications, which often worsen progressively over many years, include contractures, pain, and loss of muscle function (Stinson et al., 1991). An ED_5 dose of approximately 55 Gy (2-Gy fractions) has been estimated (Karasek et al., 1992).

2.9.3. Experimental data and mechanisms of damage

(389) Studies with irradiation of growing cartilage have shown that chondrocytes are permanently sterilised after single radiation doses of >18 Gy, and generally recover at doses of <10 Gy (Walker and Kember, 1972a,b).

(390) Animal studies show that the radiation response of bone is strongly dependent on fraction size, and α/β ratios of 4–6 Gy have been reported (Eifel, 1988; Masuda et al., 1990). Experiments with irradiation of the rat tibia show that growth retardation mainly depends on the potential growth remaining at the time of irradiation (Gonzales and Van Dijk, 1983). The postirradiation growth delay may be related to decreased local expression of parathyroid hormone-related peptide and/or Indian hedgehog (key regulators of growth plate chondrocytes) (Pateder et al., 2001; Bakker et al., 2003; Damron et al., 2004).

(391) The influence of radiation dose, sequence, and interval on bone healing has been investigated in a rat model with a standardised femoral drill hole defect (Arnold et al., 1998). With pre-operative irradiation, the adverse effect of radiation on bone healing was the same for intervals between 1 and 180 days. In contrast, while radiation during the first 3 days after surgery affected healing similarly to pre-operative irradiation, the impact was greatly reduced when radiation was given at least 4 days after induction of the bone defect. Evidence from experiments with localised and TBI, with or without BMT, suggests that postmitotic osteoclast precursor cells are of haematopoietic origin (Hosokawa et al., 2007). As irradiation affects bone viability, the stability of surgical implants is also significantly reduced in irradiated compared with unirradiated minipig bone (Verdonck et al., 2008), although the literature differs on whether or not the impairment is clinically significant (Nishimura et al., 1998; Colella et al., 2007).

(392) Studies in newborn rats suggest that radiation-induced myocyte death occurs by apoptosis (Olive et al., 1995). The apoptotic response was suppressed by cycloheximide, suggesting an association with protein synthesis. The α/β ratio for radiation-induced muscle injury was estimated to be approximately 4 Gy (Gillette et al., 1995). Whereas the multinucleated myofibres are permanently differentiated and thus incapable of mitotic activity, there is preclinical evidence suggesting that regeneration of skeletal muscle can occur by fusion of muscle stem cells (satellite cells) with injured myofibres or with each other to form new myofibres (Schultz and McCormick, 1994; Sabourin and Rudnicki, 2000). Satellite cells are probably derived from a separate population of circulating or interstitial stem cells. These cells appear to be competent to induce the regeneration of adult muscle after various types of ablative injury, including after irradiation (Adams et al., 2002; Collins et al., 2005). Muscle-derived cells also appear to have some capacity of differentiating into blood cells, and thus participate in postirradiation haematopoietic reconstitution (Pang, 2000).

2.9.4. Internal exposure

(393) Clinical data regarding effects of internal exposure of bone come from individuals exposed to radioisotopes in the occupational setting, or patients who receive therapeutic administration with radioisotopes.

(394) Internal irradiation by bone-seeking radionuclides may be categorised into volume seekers and surface seekers. Calcium, radium, and strontium represent volume-seeking elements. Volume-seeking elements may initially deposit on the surface, but are ultimately incorporated in the bone matrix. Plutonium and thorium are examples of surface-seeking elements. Surface-seeking elements accumulate on the periosteal and endosteal surfaces of the bone.

(395) The long-term effects of various radium isotopes have been studied extensively (Schmitt and Zamboglou, 1990). For example, late radiological lesions, including bone infarction, aseptic necrosis, and patchy sclerosis, were seen with a total-body ^{226}Ra burden of >0.004 MBq (Hasterlik et al., 1964). In children and adolescents, growth retardation, osteochondroma formation, and dental disorders

may occur. Preclinical work has established dose–response relationships and the impact of various isotopes on fracture tendency, fracture healing, and other pathologies (Schmitt and Zamboglou, 1990). Studies in beagle dogs indicate that overt stress fractures occurred after ^{226}Ra doses of >20 Gy or after ^{239}Pu doses of >10 Gy. In contrast, ^{90}Sr administration was not associated with fractures, even after cumulative average skeletal doses up to 135 Gy (Lloyd et al., 2001).

2.9.5. Summary

(396) The radiation effects observed in bone and skeletal muscle are predominantly late effects that appear months to years after radiation exposure. While mature bone is relatively radioresistant, growing bone is more radiosensitive, and measurable growth delay can be expected after relatively low doses of radiation. Hence, while musculoskeletal radiation effects are a minor issue in most adult patients with cancer, they remain a major problem in childhood cancer survivors.

2.10. Endocrine system

2.10.1. Anatomical features and functional organisation

(397) The endocrine system is an integrated system of small organs that involve the release of extracellular signalling hormones, which are instrumental in regulating metabolism, growth, puberty, reproduction, tissue function, and behaviour. The endocrine system consists of the central endocrine glands (hypothalamus, epiphysis, and hypophysis) and the peripheral endocrine glands (thyroid, parathyroid, and adrenal glands). Peripheral endocrine glands regulate bodily functions – such as water–salt metabolism, inflammatory and immune reactions, and reproductive function – via secretion of hormones [e.g. growth hormone (GH), prolactin, thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), LH, follicle stimulating hormone (FSH)]. The cells of the amine precursor uptake and decarboxylation system that produce biogenic amines and polypeptide hormones regulating the motility of hollow organs (e.g. the blood vessels and intestine) also belong to the endocrine system. Hormone-producing testicular cells (Leydig cells), follicular cells of the ovaries (oestrogen producers), the thymus, and the islets of Langerhans in the pancreas belong to the ‘diffuse endocrine system’. While the islets of Langerhans belong to the endocrine system, they are discussed under the gastrointestinal system as part of the pancreatic gland.

(398) Disorders of the endocrine system are commonly encountered following radiation therapy, reported in up to 50% of childhood cancer survivors, and include growth impairment, thyroid dysfunction, disrupted puberty, and infertility (Sklar, 2002). These problems may occur soon after treatment or may not present for many years. Therefore, long-term follow-up of survivors is essential to monitor, treat and, where possible, prevent morbidity.

2.10.2. Hypothalamic–pituitary dysfunction

(399) Cranial irradiation for brain tumours, nasopharyngeal carcinoma, acute lymphocytic leukaemia (ALL), or TBI in preparation for BMT may lead to hypothalamic–pituitary dysfunction (hypopituitarism) and multiple pituitary hormone deficiencies (Toogood, 2004; Agha et al., 2005; Schneider et al., 2006). The extent and timing of onset of this deficit is related to the total dose of irradiation, fractionation schedule, and time from treatment. The hypothalamus is more radiosensitive than the pituitary gland. GH is the most vulnerable anterior pituitary hormone to irradiation, followed by gonadotropin, corticotropins, and thyrotropin (Littley et al., 1989; Gleeson and Shalet, 2004). Isolated GH deficiency may develop ≥ 10 years after fractionated doses of 10–12 Gy (Holm et al., 1996; Brennan and Shalet, 2002), while higher doses (>60 Gy in 2-Gy fractions) may produce hypopituitarism (Darzy and Shalet, 2003). The frequency and severity of hypothalamic–pituitary dysfunction increase with time after irradiation due to secondary pituitary atrophy (Schmiegelow et al., 2000). Some data are indicative of increased radiosensitivity in children (Heikens et al., 1998; Agha et al., 2005).

(400) Cranial irradiation of childhood brain tumours with fractionated doses of >30 Gy in 2-Gy fractions results in GH deficiency and impaired growth in most patients, manifesting within 2 years. High fractionated-dose cranial irradiation (>54 Gy) may cause pan-hypopituitarism (Darzy and Shalet, 2003). Lower doses (<24 Gy) may be associated with precocious puberty, impaired pubertal growth spurt due to relative GH insufficiency, and reduced pubertal spinal growth (Crowne et al., 1992). Cranial fractionated irradiation with 18–24 Gy was used for the treatment of ALL between 1971 and 1990 in the UK, and was associated with GH deficiency in up to 50% of cases. TBI with lower doses of radiotherapy (7.5–15.75 Gy as fractionated dose) may also be associated with pubertal GH insufficiency, thyroid dysfunction, and radiation-induced skeletal dysplasia.

(401) Following cranial irradiation of 1–2 Gy as treatment for benign diseases occurring in childhood, a radiation-related excess of benign pituitary tumours has been shown (Ron et al., 1988). Elevated risks of pituitary adenomas have also been observed among atomic bomb survivors (Preston et al., 2002).

(402) Hyperprolactinaemia can result from irradiation of the hypothalamus at fractionated doses of >50 Gy, and this may induce suppression of the hypothalamic–pituitary–gonadal axis, resulting in hypogonadism (Sklar, 2001). Obesity may also result from cranial irradiation (>51 Gy as fractionated dose) due to damage to the ventromedial hypothalamus and GH deficiency (Cohen, 2003). No relationship has been reported between deficiency of antidiuretic hormone and irradiation of the cranium. Radiation-induced central diabetes insipidus is very uncommon.

(403) In chronic body intakes of ^{90}Sr , the pituitary is the only endocrine gland that is exposed to radiation due to its topographical proximity to the bone. Studies in rats indicate high radioresistance of the pituitary to structural damage under chronic irradiation with ^{90}Sr . Hypogonadism (cessation of oogenesis and spermatogenesis)

genesis) and hypothyroidism were only seen at accumulated doses of >150 Gy. Hyperplastic and dystrophic changes (nuclear pyknosis and lysis, disorientation of the layers of the glomerular and fascicular zones, and presence of binuclear and giant cells) were also seen in the adrenal glands of these animals (Shvedov and Akleyev, 2001).

2.10.3. Thyroid and parathyroid disorders

(404) Thyroid disorders are commonly encountered following radiation treatment for cancer, either secondary to disruption of the hypothalamic–pituitary–thyroid axis or following direct damage to the thyroid gland itself. Thyroid gland abnormalities may present as thyroid dysfunction, nodules and, rarely, thyroid cancer (Livesey and Brook, 1989; Ron et al., 1989). Central hypothyroidism with TSH deficiency may develop following cranial or craniospinal irradiation, although it is uncommon with fractionated doses of <40 Gy. However, there is some evidence to suggest that lower doses may be associated with clinically significant but subtle damage to thyrotropin secretion, despite apparently normal biochemical levels of TSH and thyroid hormone. Direct damage to the thyroid gland following radiation of the neck, at a fractionated dose of >18 Gy (Cohen, 2005), most commonly presents as hypothyroidism, with low thyroxine and elevated TSH. Risk factors are radiation dose, female sex, and older age at diagnosis, with the highest risk occurring 5 years after irradiation (Sklar et al., 2000). Hyperthyroidism may also develop from approximately 8 years after fractionated irradiation at doses of >35 Gy, but this is less common (Hancock et al., 1991; Sklar et al., 2000). Chemotherapy is an independent risk factor for thyroid dysfunction and may potentiate radiation-induced damage.

(405) Autoimmune thyroiditis has been studied among individuals exposed to low-to-moderate doses of external radiation or radioactive iodines, but the results have been inconsistent (Nagataki et al., 1994; Davis et al., 2004; Völzke et al., 2005; Imaizumi et al., 2006; Tronko et al., 2006; Agate et al., 2008). Recent studies of populations exposed to ¹³¹I from the Chernobyl accident report an association between the radiation and serum thyroid antibodies, but not with the prevalence of autoimmune thyroiditis (Tronko et al., 2006; Agate et al., 2008).

(406) Both external radiation involving the neck and radioactive iodine confer an increased risk of developing benign thyroid nodules including adenomas, focal hyperplasia, and colloid nodules. A dose–response relationship has been reported following low-to-moderate doses of radiation from treatment for benign diseases of the head and neck (Ron et al., 1989; Schneider et al., 1993), exposure from the atomic bombings (Imaizumi et al., 2006), the Chernobyl accident in Ukraine (Zablotska et al., 2008), and fallout from nuclear weapons testing in Kazakhstan (Land et al., 2008).

(407) The pathogenesis of hypothyroidism includes damaged vessels, parenchymal cell damage, and autoimmune reactions (Jereczek-Fossa et al., 2004). Experimental studies in dogs show that long-term exposure to external gamma irradiation (2.4–3.8 Gy) leads to thyroid hypofunction. A variety of structural changes (e.g. stromal

and vascular sclerosis, perivascular oedema, cord-like outgrowths of the follicular epithelium, effusion of colloid into the interstitial tissue, desquamation of epithelium, and disintegration of individual follicles) were also seen (Grigoryev et al., 1986).

(408) The risk of hyperparathyroidism increases considerably after irradiation to the neck with a long latency period of 25–47 years (Rao et al., 1980). Although the number of cases of hyperparathyroidism studied was small, a significant dose–response relationship was observed following childhood radiation treatment for benign diseases of the head and neck (Schneider et al., 1995).

2.10.4. Hypothalamic–pituitary–adrenal axis

(409) The hypothalamic–pituitary–adrenal axis has been shown to be relatively radioresistant in humans (Robinson et al., 2001). Studies in dogs also demonstrated no change in the weight of the adrenal gland 5 years after TBI with doses of 0.21–1.25 Gy/year (Grigoryev et al., 1986). However, hyperfunction was observed during the first year, including enlarged cortical matter, reduction in lipids and cholesterol, and increased enzyme activity. Dystrophic and atrophic changes were noted in the fascicular and reticular zones which increased with dose and time from irradiation (up to 2–5 years). Focal hypertrophy and hyperplasia were seen in the glomerular zone at total doses of >3.75 Gy, which may be compensatory in nature and be responsible for the development of primary aldosteronism 3–5 years after irradiation.

(410) In humans, ACTH deficiency is potentially a life-threatening condition, often with subtle onset. Although rare following low-dose cranial irradiation, ACTH deficiency must be considered in patients with pituitary tumours or those receiving fractionated cranial irradiation doses of >50 Gy (Littley et al., 1989). The insulin tolerance test is regarded as the gold standard for assessing the integrity of the hypothalamic–pituitary–adrenal axis, although severe hypoglycaemia may be problematic. Subtle clinical signs and diagnostic difficulties may lead to an underestimate of the true incidence of abnormalities of the hypothalamic–pituitary–adrenal axis. Once identified, however, life-long hydrocortisone replacement is required, and increased doses may be necessary for surgery or intercurrent illness.

2.10.5. Obesity

(411) Survivors of childhood malignancies, particularly leukaemia and brain tumours, are at risk of obesity in adulthood. Children who received cranial irradiation (18–24 Gy as fractionated dose) as part of their treatment for ALL have an increased body mass index compared with their peers, and are at risk of adult obesity (Reilly et al., 2000; Sklar et al., 2000). The aetiology of this is likely to be multifactorial (nutritional, psychological, lifestyle including lack of exercise, endocrine, and neuro-endocrine), but hypothalamic damage involving hyperinsulinism and altered leptin sensitivity may contribute. Obesity may also result from cranial irradiation (>51 Gy as fractionated dose) due to damage to the ventromedial hypothalamus

and GH deficiency (Cohen, 2003). Childhood cancer survivors treated with TBI, brain, or abdominal irradiation have an increased risk of diabetes that appears to be unrelated to body mass index or physical inactivity (Meacham et al., 2009). No relationship has been reported between deficiency of antidiuretic hormone and irradiation of the cranium.

(412) The consequences of childhood obesity are multiple, with an adverse impact on educational attainment and interpersonal relationships, especially in males. Monitoring of weight and calculation of body mass index should be performed routinely. Advice on healthy eating and exercise should be given early and reinforced regularly.

2.10.6. Hypothalamic–pituitary–gonadal axis

(413) The impact of cranial irradiation on the hypothalamic–pituitary–gonadal axis is complex, and clinical manifestations are dependent upon dose and gender of the patient. Relatively high doses of cranial irradiation may disrupt the hypothalamic–pituitary–gonadal axis resulting in hypogonadism. The hypothalamus is more radiosensitive than the pituitary gland, with hypothalamic GnRH deficiency being the most common aetiology. Fractionated radiation doses of 35–45 Gy are associated with increasingly impaired gonadotropin after irradiation (Littlely et al., 1989; Constine et al., 1993). Clinical manifestations vary from subclinical biochemical abnormalities, detectable only on GnRH stimulation, to clinically obvious delayed puberty and impaired reproductive function, which are readily treated with hormone replacement therapy. However, precocious puberty may also occur in both boys and girls after high doses of cranial irradiation for brain tumours, and this is more profound in younger patients (Ogilvy-Stuart et al., 1994). This early onset of puberty may be followed by the evolution of gonadotropin deficiency, necessitating the judicious use of gonadotropin analogues to suppress pubertal development. Early pubertal development is also associated with a premature growth spurt, early epiphyseal fusion, and reduced final adult height.

(414) In contrast, low-dose cranial irradiation (18–24 Gy in 2-Gy fractions), given to children with ALL prior to 1992, was associated with precocious puberty, predominantly affecting girls (Leiper et al., 1988). Of greater concern is the subtle decline in hypothalamic–pituitary–ovarian function that may occur with time, posing a clinical challenge. Decreased LH secretion, an attenuated LH surge, and shorter luteal phases have been reported and may herald incipient ovarian failure or be associated with early pregnancy loss (Bath et al., 2001).

(415) High-dose radiotherapy (>24 Gy as fractionated dose) for brain tumours may disrupt hypothalamic–pituitary function and result in delayed puberty, whereas lower fractionated doses (<24 Gy) are more commonly associated with precocious puberty, especially if treated when very young (Ogilvy-Stuart et al., 1994). This is most commonly seen in children who received cranial irradiation for ALL. The subsequent pubertal growth spurt can be mistaken for ‘catch-up’ growth.

2.10.7. Summary

(416) Disorders of the endocrine system are commonly encountered following radiation therapy, reported in up to 50% of childhood cancer survivors, and include growth impairment, thyroid and parathyroid disorders, obesity, disrupted puberty, and infertility. In addition, there are complex endocrine network dysfunctions in the hypothalamic–pituitary–gonadal and hypothalamic–pituitary–adrenal axes. The mechanisms are being increasingly understood, and they require hormone replacement therapies (see Section 3.3).

2.11. Nervous system

2.11.1. Anatomical features and proliferative organisation

(417) The nervous system is divided into a central part (CNS), comprising the brain and spinal cord, and a peripheral part (PNS), comprising both cranial and peripheral nerves emerging from the brain and spinal cord in pairs. The CNS is protected by the skull and vertebrae, with an additional blood–brain or blood–spinal cord barrier (BBB, BSCB) that restricts the penetration of potentially damaging chemicals from the bloodstream to the tissue. The spinal cord parenchyma consists of a cortex of white matter (nerve fibres sheathed by fatty myelin, microvasculature, and glial cells) and a central butterfly-shaped region of grey matter (neuronal cell bodies and glial cells). The cerebellum of the brain has the opposite arrangement, with the grey matter forming the outer cerebral cortex and the mass of fibre tracts forming the white matter in the central core.

(418) There are two major parenchymal cell types in the CNS, both of neuroectodermal origin: the neurons (structural subunits and FSUs of the nervous system) and the supportive glial cells. Connective tissue and fibroblasts are not found in the CNS, except in association with major blood vessels. Neurons are highly differentiated and lose their capacity to proliferate shortly after birth. Glial cells (astrocytes, oligodendrocytes) retain their capacity to divide, although cell turnover is normally very slow (>200 days in adults) (Schultze and Korr, 1981; Van der Kogel, 1986). Astrocytes provide a supportive role for the neurons and are involved in tissue repair. They also participate in transmission of neuronal signals, and in formation and maintenance of the BBB. Oligodendrocytes are involved in formation and maintenance of the myelin sheath surrounding neurons, which permits efficient propagation of nerve pulses. Each oligodendrocyte is connected to numerous myelin segments by cytoplasmic processes. Microglia were originally classified as glial cells, but they actually develop from monocytes and not from neural progenitor cells. These cells have phagocytic properties and are thought to act as a type of macrophage in the CNS in response to injury. In the PNS, Schwann cells are involved in myelination and regeneration of peripheral nerves and, in contrast to oligodendrocytes, each Schwann cell is connected to a single myelin segment.

(419) The subependymal plate is a vestige from embryonal brain development, and this remains mitotically active throughout adult life. In the rest of the CNS,

both glial and endothelial cells are normally quiescent, with a small growth fraction and long cell turnover times. However, these cells can respond to injury, including radiation, by marked increases in proliferation. Various animal studies have shown a transient increase in cellular proliferation and the number of oligodendrocytes during the first 1–2 months after spinal cord irradiation. This is followed by a sharp decline in cell number immediately prior to the onset of necrosis (at 3–4 months after irradiation), with a second wave of proliferation after the onset of necrosis (Van der Kogel, 1986). The early wave of proliferation is probably in response to apoptotic cell loss and segmental demyelination after radiation, whereas the second proliferative burst occurs in response to white matter necrosis.

2.11.2. Clinical data on high-dose exposures and therapeutic doses

Clinical syndromes

(420) High total-body exposures of 10–20 Gy will induce a neurovascular syndrome within 1–72 h (Dainiak et al., 2003), which will lead to death within a few days. Some of the early symptoms (nausea and vomiting) are gastrointestinal, but these and other symptoms (e.g. hypotension, fever, headache, neurological and cognitive deficits, and cardiovascular collapse) occur before the onset of toxicity in the gastrointestinal and haematopoietic systems.

(421) High-dose therapeutic irradiation can cause injury to the CNS, eventually resulting in paralysis. Conservative dose constraints are therefore usually applied for the CNS when treating tumours of the head and neck, thoracic and upper abdominal malignancies, and brain tumours. Injury is manifest in three phases. During radiotherapy of the brain (especially high-dose stereotactic radiotherapy), patients may experience fatigue and neurological symptoms, including seizures, although symptoms are usually reversible. These acute effects are due to endothelial cell apoptosis with disruption of the BBB and secondary oedema. A delayed, sensory reaction, called ‘Lhermitte’s syndrome’, may develop 2–4 months after irradiation of the spinal cord. This is characterised by limb weakness, clumsiness, and a tingling sensation in the back and extremities. After cranial irradiation, somnolence may occur during this period. Transient, segmental demyelination, caused by early apoptotic death of oligodendrocytes, is the likely mechanism for these reactions, which generally resolve within a few months.

(422) In contrast to the acute and early delayed reactions, late effects, with a latency of at least 6 months, are irreversible. In the spinal cord, such damage leads to permanent motor and sensory defects, including paralysis (myelopathy). The underlying pathology of late radiation injury is demyelination and white matter necrosis, with various vascular lesions (telangiectasia, focal haemorrhage) in both white and grey matter (Schultheiss et al., 1995; Tofilon and Fike, 2000; Wong and Van der Kogel, 2004; Nieder et al., 2007b). In the brain, late radiation injury manifests as minor to severe cognitive defects and memory impairment. Learning disabilities in children and cognitive impairment in adults have been shown to correlate

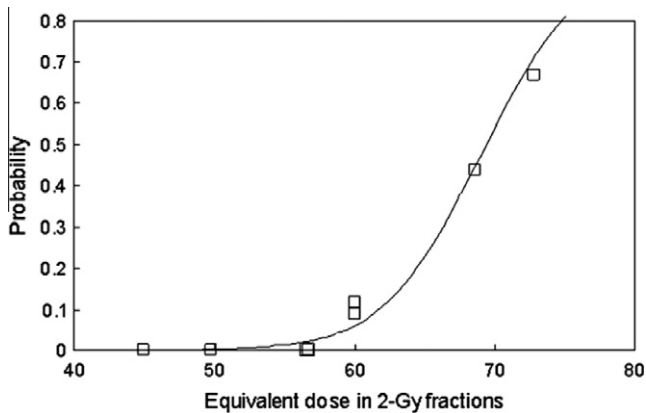


Fig. 2.12. Estimated probability of exceeding cervical cord tolerance (myelopathy) as a function of total iso-effective (equivalent) dose in 2-Gy fractions (Schultheiss, 2008).

with the severity of white matter changes (Constine et al., 1988), but can also occur in the absence of apparent structural lesions.

Tolerance doses

(423) The spinal cord is more radioresistant than some other late-responding tissues (e.g. lung, heart, and kidney), but the consequences of exceeding tolerance can be so severe that conservative dose restraints of 45–50 Gy (total fractionated dose) are generally applied in radiotherapy where the cord is involved. Analysis of the clinical data indicates that conventional, daily fractionated schedules with total doses of <50 Gy (2-Gy fractions) are associated with a very small risk of radiation myelopathy (<0.5%) in the absence of chemotherapy or other predisposing factors (Marcus and Million, 1990; Wong et al., 1994; Schultheiss et al., 1995; Schultheiss, 2008).

(424) Estimated doses for a 5% incidence of myelopathy are 57–61 Gy to the cervical cord (2-Gy fractions), with a steep rise in the probability of damage above these doses (Fig. 2.12). Some analyses indicate that the thoracic cord is less sensitive than the cervical cord, with a less steep dose–response curve (Schultheiss, 2008).

(425) Similar tolerance estimates are derived from data on radiation injury to the lumbosacral nerve roots (cauda equina), although much less information is available. Emami et al. (1991) gave estimated doses of 60 Gy for 5% toxicity in the cauda equina (in doses of 1.8–2.0 Gy), and more recent analyses indicate ED₅ tolerance doses of 55 Gy for males and 67 Gy for females at 5 years, decreasing to 47 Gy and 58 Gy, respectively, at 10 years (Pieters et al., 2006).

(426) Brain necrosis in adults is rare for conventionally fractionated total doses of <60 Gy in radiotherapy, although neurocognitive defects are seen at considerably lower doses. Cognitive impairment, including dementia, occurs in 20–>50% of adult patients with brain tumours who survive for >1 year after treatment with large field irradiation to total doses of 40–60 Gy (Crossen et al., 1994). Declines in intelligence

quotient (IQ) scores with time from treatment have been reported in children treated with ALL given low-dose prophylactic whole-brain irradiation (24 Gy in 2-Gy fractions), and in children with brain tumours treated with cranial doses of 23–36 Gy, excluding tumour boost (Mulhern et al., 1992, 2004; Langer et al., 2002). A review of the clinical literature shows that the rate of IQ decline is associated with young age at time of treatment, follow-up time, and radiation dose (Mulhern et al., 2004). Concomitant chemotherapy is often used in treating these children, and this is likely to contribute to the cognitive impairment. An analysis of adult survivors of childhood cancers of the CNS ($n = 1877$) demonstrated significantly elevated risks of neurocognitive impairment and reduced socio-economic outcomes compared with sibling controls ($n = 3899$) (Armstrong et al., 2009). Survivors had significantly impaired attention spans and memory, as well as problems with organisation and emotional regulation. These impairments were related to cranial radiation doses (when comparing those with no cranial radiation, <50 Gy, and >50 Gy total fractionated dose) for treatment of astrocytoma, glial tumours, or ependymoma, but there was no clear dose–response relationship for medulloblastoma.

(427) One of the most important factors influencing the tolerance dose of the spinal cord is the size of the dose per fraction. Early clinical studies using fractions of 4–6 Gy resulted in considerable numbers of patients with myelitis after relatively low total doses of 35–40 Gy (Abramson and Cavanaugh, 1973; Dische et al., 1981; Fitzgerald et al., 1982). Analysis of radiation myelopathy data yielded an α/β ratio of 0.87 (95% CI 0.54–1.19) Gy for human cervical cord (Schultheiss, 2008; Kirkpatrick et al., 2010). This is consistent with experimental animal studies showing that the spinal cord has a low α/β ratio of 2 Gy (see below).

(428) The spinal cord is a slow turnover tissue and variations in overall treatment time (e.g. from 3 to 7 weeks) would not be expected to markedly influence tolerance doses. However, accelerated and hyperfractionated radiation schedules using multiple fractions per day have led to incidences of myelitis at total doses well below the tolerance estimates quoted above (Dische and Saunders, 1989; Wong et al., 1991). Incomplete repair between multiple fractions per day is the likely explanation for these toxicities, although other factors cannot be excluded (Thames et al., 1988). Experimental data on spinal cord injury in animal models (see below) suggest that the tolerance dose decreases by approximately 15% when the interval between fractions is reduced from 24 to 6 h (Schultheiss et al., 1995).

(429) Although it is generally accepted that the dose to the spinal cord should be reduced for large field sizes, there is actually very little clinical data to demonstrate significant volume effects in the spinal cord. Animal data (see below) do indicate a significant volume effect for spinal cord at higher incidences of damage, but much less than for other tissues such as lung and liver. At low probabilities of injury, which usually define clinical tolerance doses (<5% incidence of injury), the slope of the dose–response curve is shallow and a volume effect may not be detectable.

(430) In contrast, clear volume effects are discernable in irradiated brain, both for clinical side-effects and changes in structure detected using neuro-imaging

(Levegrun et al., 2001). For example, after stereotactic radiosurgery for arteriovenous malformations, the volume of brain irradiated to 10 Gy was found to be significantly correlated with imaging changes (Voges et al., 1996). Whether or not such changes lead to clinical symptoms depends strongly on the location of the damage. Tissue structural changes in the midbrain and brainstem seem to be most often associated with clinical symptoms after stereotactic radiosurgery (Flickinger et al., 1992). Data on long-term effects of fractionated partial-brain radiotherapy with 3D treatment planning (for quantification of volumes) are rare. However, the risk of brainstem toxicity in patients with skull base chordomas was shown to be significantly associated with the volume treated with doses of >60 Gy (Debus et al., 1997). There was also a non-significant trend for higher rates of temporal lobe damage in patients with tumour volumes of >70 cm³ vs <70 cm³ (31% and 7%, respectively) (Santoni et al., 1998).

2.11.3. Experimental data and mechanisms of damage

Acute damage

(431) The earliest histopathological sign of radiation injury in the CNS is diffuse nodal widening and segmental white matter demyelination, due to loss of oligodendrocytes, which occurs within 2 weeks after single doses of >5 Gy (Mastaglia et al., 1976; Van der Kogel, 1986). This acute injury is preceded by increased inflammatory gene expression [e.g. nuclear transcription factor κ B (NF κ B), TNF α , and IL-1 β] which has been demonstrated within hours of irradiation of rodent CNS (Hong et al., 1995; Raju et al., 2000; Tofilon and Fike, 2000; Gaber et al., 2003; Wong and Van der Kogel, 2004). TNF α is a key regulator of ICAM-1, which is associated with BBB or BSCB disruption after a variety of injuries. In irradiated mouse brain, the early, dose-dependent increase in ICAM-1 expression was paralleled by increased induction of haem oxygenase 1, a marker of oxidative stress, and subsequent neuronal death (Calingasan et al., 2000). Increased expression of ICAM-1 after spinal cord irradiation in rats was predominantly in the vascular endothelium and colocalised with regions of BSCB disruption (Nordal and Wong, 2004).

Late effects

(432) Focal demyelination of the spinal cord develops from approximately 4–6 months after high radiation doses (>20 Gy as single dose); latency is inversely related to dose. This rapidly progresses to tissue necrosis and the onset of paralysis. Vascular lesions (oedema, thrombosis, and haemorrhage) are apparent at this time, particularly after high doses, and this has been proposed as the precipitating factor for white matter necrosis (Van der Kogel, 1986). At longer times after lower radiation doses (1–2 years in rats), telangiectasia and haemorrhagic infarcts develop in both irradiated spinal cord and brain. Spinal cord necrosis does not occur in the caudal equina, even after high radiation doses. The damage at this site is restricted to demyelination and necrosis of the nerve roots, associated with loss of Schwann cells (Van der Kogel, 1986).

Cognitive impairment

(433) Irradiation of whole brain with single doses as low as 4.5 Gy has been shown to significantly impair memory and motor function in mice, whereas a dose of 1.5 Gy had no behavioural effects (Martin et al., 2001). It has recently been shown that cognitive impairment after whole-brain irradiation of rats is associated with alterations in the N-methyl-D-aspartic acid receptor subunits, important for synaptic transmission, and that these changes can occur in the absence of neural degeneration (Shi et al., 2006, 2008). Other behavioural studies in mice suggest that impaired memory and motor activities are related to cerebral oxidative stress (Manda et al., 2007) and impairment of hippocampal neurogenesis in young mice (Rola et al., 2004). Studies in rats showed that the memory defects at 9 months after 40 Gy in 5-Gy fractions were preceded by a significant decrease in capillary density, suggesting that the cognitive impairment may be a form of vascular dementia (Brown et al., 2007).

Vascular vs parenchymal targets for radiation injury

(434) The documented association between disruption of the BBB (or BSCB) and both acute and late radiation toxicity implicates endothelial cells as important targets (Rubin et al., 1994; Nordal and Wong, 2005). Indeed, dose-dependent loss of endothelial cells has been demonstrated in irradiated brain and spinal cord within 24 h of exposure (Ljubimova et al., 1991; Li et al., 2004). This acute apoptotic response is independent of p53, but dependent on the acid sphingomyelinase (ASMase) pathway (Li et al., 2003). Irradiation of ASMase knockout mice did not result in either endothelial cell apoptosis or disruption of the BSCB, whereas p53 knockout mice responded similarly to wild-type mice. In contrast, the apoptotic response of oligodendrocytes (also seen within 24 h of irradiation) was dependent on p53 and not ASMase (Li et al., 1996; Chow et al., 2000). Taken together, these results suggest that endothelial cell apoptosis, rather than oligodendrocyte apoptosis, is involved in the acute disruption of the BSCB after irradiation, and that the trigger is probably induced inflammatory cell expression and oxidative stress. According to this model, oligodendrocyte apoptosis and focal demyelination occur as a secondary consequence of these events (Hopewell and Van der Kogel, 1999).

(435) The apoptotic response of oligodendrocytes, initiated within 24 h of spinal cord irradiation, results in a dramatic loss of oligodendrocyte progenitors (O2A cells) at 2–4 weeks after single doses of >15 Gy to the rat spinal cord, followed by a dose-dependent recovery by 3 months after irradiation (Hopewell and Van der Kogel, 1999). This leads to a transient, focal demyelination which is associated with Lhermitte's syndrome in humans. However, there appears to be a poor relationship between glial cell survival and the subsequent development of radiation myelopathy. Damage to the vasculature seems to be a much more important determinant of late damage. This was illustrated in experiments where rat spinal cord was irradiated by boron neutron capture therapy, using capture agents that did or did not pass the BBB (Coderre et al., 2006). For total radiation doses that gave equivalent incidences of white matter necrosis and myelopathy, there was a much

higher survival of O2A progenitors when the irradiation was selectively delivered to the endothelium, reflecting the lower dose delivered to the parenchymal cells. The doses required to induce myelopathy related to the dose delivered to the vasculature and not the dose delivered to the parenchyma or to O2A progenitor survival.

(436) Working models for radiation response in the CNS have been proposed incorporating both vascular and parenchymal components. According to these models, radiation induces direct cell death (apoptosis) in several populations (endothelial cells, glial progenitors, and oligodendrocytes), and activates a series of cytokine cascades, resulting in reactive processes and persistent oxidative stress, with secondary tissue injury and neurological defects (Tofilon and Fike, 2000). Early apoptosis of endothelial cells leads to breakdown of the BBB and transient, acute CNS injury, whereas delayed mitotic endothelial cell death results in late-onset breakdown of the BBB, white matter necrosis, and permanent late CNS injury (Wong and Van der Kogel, 2004; Nordal and Wong, 2005).

Fractionation effects

(437) Extensive experimental data on the influence of fractionation schedules on radiation tolerance show that the spinal cord has a high capacity for repair of sub-lethal damage, with α/β ratios of approximately 2 Gy for cervical cord and 3–5 Gy for lumbar cord (White and Hornsey, 1978; Ang et al., 1983; Van der Kogel, 1986; Thames et al., 1988; Wong et al., 1995). The size of the dose per fraction is therefore of great importance in determining tolerance of the spinal cord, with high doses per fraction resulting in much greater damage and lower tolerance doses. In contrast, the overall treatment time has little influence on tolerance dose in this slow turnover tissue, for daily fractionated radiotherapy given in total times not exceeding 8 weeks (White and Hornsey, 1980; Van der Kogel et al., 1982). For multiple fractions per day, incomplete repair between fractions may lead to increased damage compared with single fractions per day. Analysis of repair half-times from experimental studies in rodents indicates bi-exponential repair kinetics, with fast- and slow-component half-life values of 0.2–0.7 and 2.2–6.4 h, respectively (Ang et al., 1992; Landuyt et al., 1997; Pop et al., 1998). As a consequence of the slow component of repair, spinal cord tolerance decreased by 16% for interfraction intervals of 6 h compared with 24 h.

(438) Despite its slow turnover rate, the spinal cord is capable of substantial long-term recovery over periods of several months to years. This was illustrated in re-irradiation studies, where the total doses required to induce myelopathy (initial plus retreatment) for re-irradiation at 4–6 months (rodent studies) or 2 years (monkey studies) increased to $\geq 140\%$ of biologically equivalent tolerance doses in single-course schedules (Ang et al., 1993; Wong and Hao, 1997). Additional studies with monkeys demonstrated that further long-term recovery took place in the spinal cord as retreatment intervals increased from 1 to 3 years; the estimated total doses for initial plus retreatment doses at 3 years amounted to $>160\%$ of the single-course tolerance dose (Ang et al., 2001). It is possible that increased proliferation of O2A glial progenitor cells may have contributed to this recovery (Van

der Maazen et al., 1992), but the lack of correspondence between glial cell survival and myelopathy (Coderre et al., 2006) implies that other factors must also be involved.

Volume effects

(439) Experiments in rats have demonstrated a marked increase in tolerance dose for irradiation of very short lengths of spinal cord (<1 cm). This is due to inward migration of surviving cells, over very short distances, from the surrounding unirradiated area (Hopewell and Trott, 2000). Further evidence for this comes from studies using a high-precision proton beam for irradiation of a single field of 8 mm or two fields of 4 mm, separated by an unirradiated length of cord (Bijl et al., 2003, 2006). ED₅₀ for myelopathy with 2 × 4-mm fields was the same as for a single 4-mm field, and considerably greater than for an 8-mm field. The marked volume effect for irradiation of very short lengths of spinal cord was compromised by small doses given to the surrounding tissue, suggesting that migration of cells into the high-dose region was inhibited by the low dose to surrounding tissue.

(440) Studies in pigs and monkeys demonstrate a much smaller volume effect for field sizes of 1–10 or 4–16 cm (Schultheiss et al., 1994; Van den Aardweg et al., 1995). In the studies with monkeys (Schultheiss et al., 1994), the incidence of myelopathy increased from 15% to 20% to 37.5% for total fractionated doses of 70 Gy to field sizes of 4, 8, and 16 cm; this is consistent with probability models. Since the dose–response relationships for myelitis are steep, such relatively small volume effects are unlikely to be detectable at the low probabilities of injury (<5%) that are clinically relevant.

(441) Significant volume effects were seen in dogs for functional neurological symptoms (pain and paresis) after irradiation of 4- or 20-cm lengths of spinal cord (ED₅₀ of 78 and 54 Gy, respectively). Much less pronounced volume effects were, however, seen for morphological necrotic lesions (Powers et al., 1998).

2.11.4. Exposure to doses of <5 Gy

(442) Between 1940 and 1960, irradiation of the scalp was extensively used in treatment of children (mean age 7–8 years) with *Tinea capitis* (ringworm). Brain doses were in the range of 0.7–1.75 Gy. Several epidemiological and functional studies have been carried out on these subjects to investigate the long-term effects of low-dose cerebral irradiation on mental function. Long-term follow-up (average 20 years) of 2215 irradiated subjects and 1395 non-irradiated subjects treated for *Tinea capitis* at New York University Hospital demonstrated a 40% excess of treated psychiatric disorders in the irradiated White American patients, but no difference in Black Americans (Shore et al., 1976). Psychiatric and psychometric analysis of a subgroup of 177 irradiated and 68 unirradiated subjects confirmed an increase in psychiatric symptoms and more deviant scores in the irradiated White group, although the overall rating of psychiatric status only showed borderline differences (Omran et al., 1978).

(443) In a larger study on 11,000 irradiated Israeli subjects and 11,000 population controls, the irradiated children (mean brain doses of 1.3 Gy) were also found to have lower IQ and psychological scores, and a slightly higher incidence of mental retardation (Ron et al., 1982). A separate analysis of visual evoked responses on 44 irradiated and 57 controls also showed significant differences between the groups (Yaar et al., 1980).

(444) A population-based cohort study of 3094 men who were irradiated for cutaneous haemangioma before 18 months of age reported that intellectual development was adversely affected by radiation doses of >0.10 Gy (Hall et al., 2004). The proportion of boys attending high school decreased with increasing dose of radiation, from 32% among those not irradiated to 17% in those who received >0.25 Gy. Comparing these two groups, the multivariate OR for high school attendance was 0.47 (95% CI 0.26–0.85) for irradiation to the frontal part of the brain, and 0.59 (95% CI 0.23–1.46) for irradiation to the posterior brain.

(445) Taken together, the results of these studies indicate that low-dose irradiation (<1 – 2 Gy) to the immature developing brain can cause long-term cognitive and behavioural defects.

(446) Analysis of the incidence of dementia among atomic bomb survivors did not demonstrate any relationship between radiation exposure and development of dementia in subjects exposed to doses of ≤ 4 Gy at ≥ 13 years of age (Yamada et al., 2009). The incidence of dementia was between 15 and 17 per 10,000 person-years for exposure doses of 0.005, 0.005–0.50, and >0.50 Gy.

2.11.5. Summary

(447) Spinal cord is relatively radioresistant, but the consequences of exceeding tolerance are so severe (paralysis) that conservative dose constraints of 45–50 Gy (total fractionated dose) are usually applied. Dose per fraction is the most important determinant for risk of myelitis. Overall treatment time and volume irradiated have less influence. Doses required to induce myelopathy correlate with dose delivered to the vasculature and endothelial cell damage rather than dose delivered to the parenchyma and glial damage.

(448) Brain necrosis is rare after total fractionated doses of <60 Gy, but significant cognitive impairment can develop after much lower doses (<1 Gy), especially after exposure in childhood. Disruption of the BBB is associated with both acute, transient tissue damage and late, progressive tissue damage.

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3. MODIFIERS OF NORMAL TISSUE RESPONSE

3.1. Terminology

(449) Modifiers of normal tissue radiation responses are generally referred to as prophylactic agents/radioprotectors, mitigators, or therapeutic agents (Stone et al., 2004). Radiation prophylactic/protective agents are given before exposure and are usually antioxidants or free radical scavengers that prevent fixation of the initial radiochemical event and/or eliminate an early cascade of inflammatory/oxidative reactions consequent to the initial event. Mitigators, on the other hand, are given shortly after radiation exposure, before clinical presentation of radiation injury, while therapeutic agents are administered after development of overt symptoms. All three classes of agents have been tested in preclinical and clinical studies focused on reducing normal tissue side-effects in cancer patients who undergo radiation therapy. Among the radioprotective agents, the free radical scavenger amifostine is perhaps best known and most studied. Mitigating agents include, for example, angiotensin-converting enzyme (ACE) inhibitors, which have been used in the mitigation of lung, renal, nerve, and other organ injuries. Examples of therapeutic agents include the combination of pentoxifylline and vitamin E, which appears to ameliorate, and even reverse, fibrosis in skin and some internal organs (e.g. heart).

(450) While the terminology is useful, it is important to keep a few details in mind. Firstly, classification of protectors, mitigators, and therapeutics applies not only to the cancer treatment situation, but also to scenarios of radiation accidents and radiological/nuclear terrorism. However, an agent that is an effective modifier of the radiation response in an organ exposed to high doses of fractionated radiation therapy may not be effective in the situation where the whole body is exposed to moderate doses of radiation and where injury occurs in several organ systems. Secondly, the distinction between protectors, mitigators, and therapeutics is not always clear. For example, while free radical scavengers and antioxidants are most effective when given at the time of irradiation, they also appear to have an effect when administered after exposure because they affect the postradiation oxidative stress. Somatostatin analogues, which inhibit pancreatic secretion and granulocyte transmigration in damaged intestine, appear to be equally effective when used as protectors and mitigators. Finally, certain agents (e.g. some immunomodulators and agents that exert a trophic effect on normal tissues) may actually have opposite effects when given before radiation exposure compared with afterwards. This is a complex and rapidly evolving field; therefore, the following sections will only discuss selected modifiers of radiation responses.

3.2. Mechanisms of action

3.2.1. Antioxidants

(451) ROS are normally controlled by the antioxidant defence system including glutathione and antioxidant enzymes: manganese superoxide dismutase (MnSOD), copper–zinc superoxide dismutase (CuZnSOD), catalase, and glutathione peroxidase. Antioxidants also regulate the level of nitrogen oxide and formation of lipid peroxidation products. Glutathione and the enzymes MnSOD and CuZnSOD are the most important intracellular antioxidants. SOD enzymes (Delanian et al., 1994; Lefaix et al., 1996), various SOD mimetic small molecule compounds (Rong et al., 1999; Salvemini et al., 1999; Vujaskovic et al., 2002a; Muscoli et al., 2003; Rabbani et al., 2007; Gauter-Fleckenstein et al., 2008), and delivery of the *SOD* gene (Stickle et al., 1999) have been explored as agents to reduce the adverse effects of radiation therapy on normal tissues, as well as the effect of total- or partial-body irradiation in the setting of a nuclear accident or radiological/nuclear terrorism scenario (Kumar et al., 1988).

(452) Radiation exposure, even at low doses, causes changes in the activity of antioxidant enzymes (Durovic et al., 2008; Klucinski et al., 2008). The redox-sensitive NF κ B is activated after exposure to small doses of radiation and this results in increased *MnSOD* gene expression, enzyme activity, and cell radiosensitivity (Murley et al., 2008).

(453) The high intrinsic radiosensitivity shown by some cell lines is associated with disturbed antioxidant activity (Tulard et al., 2003). Downregulation of antioxidant enzymes is also a determinant in the process of neoplastic transformation. Both effects are related to decreased MnSOD, glutathione peroxidase, and glutathione (Bravard et al., 2002). The protective effect of antioxidants has been demonstrated in experimental studies *in vitro* and *in vivo*, as well as in the clinic. Dietary and endogenous antioxidants are known to protect tissues against radiation damage (Prasad, 2005).

(454) An antioxidant can exert its action directly or indirectly. Antioxidants can directly scavenge hydroxyl radical, peroxy radical, peroxy nitrite anion, and singlet oxygen, thereby protecting cell membranes, proteins in the cytosol, and DNA in the nucleus (Shirazi et al., 2007). Cyclic nitroxides exert radical scavenging activity via complex mechanisms, including direct protection against radiation-induced radicals, SOD mimetic action, inhibition of lipid peroxidation, conferring catalase-like behaviour to haem proteins, and inhibition of the Fenton reaction. Antioxidants exert a protective action against the cytotoxic and mutagenic effects of ROS, and cellular protection against oxidative damage (Soule et al., 2007). Other antioxidants, such as melatonin, also increase the activity of some important antioxidant enzymes, and decrease the activity of nitric oxide synthase, a pro-oxidative enzyme (Shirazi et al., 2007).

(455) Some of the naturally occurring antioxidants, such as vitamin E or selenium, may be less effective radioprotectors than synthetic antioxidants, but they can provide longer protection against adverse effects of low-dose and low-dose-rate expo-

tures to ionising radiation, including when administered after irradiation. Natural antioxidants have a potential for multiple physiological effects, as well as antioxidant activity (Weiss and Landauer, 2003). Combinations of antioxidants may be more effective than single agents (Prasad, 2005).

3.2.2. Thiols and radical scavengers

(456) Induction of free radicals is one of the earliest cellular events to occur after ionising radiation, and radical scavengers (e.g. cysteine) have been recognised as potent radiation protectors for >50 years. These compounds are effective when given before irradiation and, as they react with free radicals in competition with oxygen, the degree of radioprotection is highly dependent on oxygen tension, being maximal at intermediate oxygenation (Denekamp et al., 1982). Out of >4000 thiol compounds specifically investigated for their radioprotective potential at the Walter Reed Army Institute of Research in the USA, amifostine (WR-2721) emerged as the best drug in terms of efficacy to toxicity ratio. Amifostine is rapidly dephosphorylated to its active metabolite WR-1065, either by hydrolysis at low pH or by a catalysed reaction involving alkaline phosphatase at higher pH. The presence of the active metabolite in normal tissues varies considerably, with very high uptake in salivary glands and intestinal mucosa, and lower uptake in tumours. Amifostine and its metabolites do not cross the BBB, so protection is not seen in the CNS. These differences in uptake of the active metabolite may depend on differential activity of alkaline phosphatases in blood vessels of normal tissues and tumours, and on dephosphorylation activity. There are also wide variations in the maximum degree of radioprotection seen among normal tissues, ranging from protection factors of ≤ 3.0 in salivary gland to <1.5 in bladder and kidney. In addition to drug uptake and clearance rates, and differential dephosphorylation activity between tissues, factors such as oxygen tension will influence the extent of radioprotection. Although amifostine is generally considered to be preferentially taken up and activated in normal tissues, some pre-clinical data in rodent models and canine tumours have demonstrated significant levels of radioprotection, especially in smaller, non-hypoxic tumours and after fractionated irradiation (Denekamp et al., 1983; McChesney et al., 1988; Andreassen et al., 2003).

(457) Although the main mechanism of radioprotection is via radical scavenging, WR-1065 can also react directly with oxygen, thereby inducing local hypoxia. Thiols may also facilitate repair processes by donation of hydrogen, and decrease the accessibility of ionisation sites by inducing DNA packaging. Side-effects of amifostine include hypotension, vomiting, and allergic reactions (Lindegaard and Grau, 2000; Andreassen et al., 2003).

(458) Amifostine has been shown to reduce the incidence of early and delayed radiotherapeutic injury at several anatomical sites, but the practicalities of administering the drug 30 min prior to each radiation exposure, high cost, side-effects, and lingering doubt regarding the absence of tumour protection have hampered its widespread clinical use.

3.2.3. Inhibitors of apoptosis

(459) Some cell populations in normal tissues are sensitive to the induction of apoptosis by ionising radiation and other DNA-damaging agents. These include specific cell stages and types within the following cell populations: thymocytes, lymphocytes, spermatogonia, hair-follicle cells, stem cells of the small intestine and bone marrow, and tissues in developing embryos. Apoptosis is an active process requiring protein synthesis, and is highly cell-type specific (Elmore, 2007). Agents that reduce the incidence of radiation-induced apoptosis in different cell types include radical scavengers and antioxidants, cytokines and growth factors, inhibitors of p53-mediated pathways of response, and inhibitors of the action of caspases in the apoptotic process (Brown and Attardi, 2005; Meyn et al., 2009).

3.2.4. Anti-inflammatory agents

(460) Irradiation causes excessive production of eicosanoids (prostaglandins, prostacyclin, thromboxane, and leukotrienes), which are endogenous mediators of inflammatory reactions such as vasodilation, vasoconstriction, vascular permeability, microthrombus formation, and extravasation of leukocytes. Experimental studies in animal models have shown increased levels of endogenous prostaglandins and thromboxanes, persisting for weeks to months after irradiation of a wide range of organs and tissues. The one exception is the irradiated aortic wall which has a reduced ability to synthesise prostacyclin (Michalowski, 1994). Glucocorticosteroids inhibit excess eicosanoid synthesis, mainly by inhibition of phospholipase A₂ activity and synthesis, thereby inhibiting release of arachidonic acid (the precursor of prostanoids and leukotrienes) from cell membranes. Non-steroidal anti-inflammatory drugs (NSAIDs) work via inhibition of cyclo-oxygenase, which specifically catalyses prostanoid synthesis without affecting leukotriene synthesis. Most NSAIDs are reversible competitive inhibitors of arachidonic acid binding to cyclo-oxygenase, but aspirin causes irreversible inhibition of the enzyme. In appropriate doses, aspirin gives selective inhibition of pro-thrombotic platelet thromboxane with much less inhibition of endothelial-cell-derived prostacyclin.

(461) Most cell types can synthesise diffusible eicosanoids; therefore, disturbances in vascular haemodynamics, permeability, and thrombotic or inflammatory status after irradiation are due to both direct effects on endothelial cells and indirect effects from diffusible mediators produced by other irradiated cells.

(462) Eicosanoids are formed from polyunsaturated fatty acids (PUFAs), which cannot be synthesised but are derived from the diet. There is some evidence that modifications in dietary PUFAs can have a beneficial effect in irradiated tissues by shifting the balance of eicosanoid synthesis in the anti-inflammatory direction (Hopewell et al., 1994a,b; Moulder et al., 1998). In particular, gamma-linolenic acid inhibits the production of inflammatory leukotrienes and increases the production of prostaglandin E₁ (PGE₁) and thromboxane A₁. PGE₁ has anti-inflammatory, anti-thrombotic, and vasodilatory properties, and thromboxane A₁ does not have the

prothrombotic properties of thromboxane A₂. Eicosapentaenoic acid also selectively increases prostaglandins at the expense of thromboxanes.

3.2.5. ACE inhibitors and modulation of the renin–angiotensin system

(463) The renin–angiotensin system plays a key role in the regulation of haemodynamics in the kidney, lung, and circulatory system. In this negative feedback loop, decreases in arterial blood pressure stimulate renin release by the kidney and this cleaves angiotensin to angiotensin I (Ang I), which is converted by ACE to the potent vasoconstrictor Ang II, thereby raising blood pressure. Ang II also stimulates aldosterone secretion to promote salt retention, which further increases blood pressure, switching off the stimulus for renin release. Suppression of the renin–angiotensin system, either using ACE inhibitors or AII receptor antagonists, has been shown to be effective in reducing or preventing functional damage in irradiated kidney, lung, and skin (Moulder et al., 1998, 2007). Antihypertensive mechanisms may be involved in reducing established nephropathy, but this cannot fully explain the protection seen in other organs, or the inhibition of development of radiation nephropathy, since other types of antihypertensives are not effective in protecting against radiation injury when given prophylactically.

(464) Thiol-containing ACE inhibitors, such as captopril, are widely used in the treatment of hypertension, but they also have other properties such as radical scavenging and protection of endothelial cell function in irradiated tissues (Ward et al., 1988, 1992). Captopril also prevents the radiation-induced decrease in nitric oxide activity in irradiated kidneys, and AII receptor antagonists prevent radiation-induced increases in TGF- β , which may contribute to their efficacy in inhibiting fibrosis in irradiated tissue. Ang II is also a potent pro-inflammatory agent, mediating the release of adhesion molecules and inflammatory cytokines via activating protein-1 and NF κ B. Inhibition of Ang II in irradiated tissue therefore probably also exerts an anti-inflammatory effect (Robbins and Diz, 2006). Other possible mechanisms for the protective effects of inhibition of the renin–angiotensin system in irradiated tissue include suppression of oxidative stress and suppression of aldosterone, which promotes fibrosis in non-irradiation models, or direct inhibition of fibroblast proliferation (discussed in Moulder et al., 2007).

3.2.6. Growth factors and cytokines

(465) HGFs and non-HGFs (GFs) and cytokines act through specific cell-surface receptors on target cells to induce a variety of responses including survival, proliferation, self-renewal, and differentiation (Kaushansky, 2006). Proliferation and survival may be initiated through reducing the level of cell-cycle inhibitors and increasing the anti-apoptosis protein BCLXL. Granulocyte colony-stimulating factor (G-CSF), for example, supports survival, proliferation, self-renewal, and differentiation of granulocyte progenitor cells, as well as survival and function of mature cells throughout the granulocyte lineage. The extrinsic or intrinsic action of HGFs has

been the focus of debate. A recent study by Rieger et al. (2009) demonstrated that G-CSF and macrophage colony stimulating factor (M-CSF) can instruct haematopoietic lineage choice. These investigators used a bio-imaging approach to show that signal transduction pathways from cell-extrinsic cytokines can influence the intracellular lineage commitment.

(466) The capacity of HGFs, GFs, and cytokines to function in situ depends upon their concentration, timing, interaction with other GFs and cytokines, receptor modulation on target cells, physiological half-life, and interaction with other stromal cells within the lineage or stem-cell-selective micro-environmental niche.

3.2.7. Modifiers of endothelial cell response

(467) Radiation induces profound changes in the microvascular endothelium. These changes have been shown to play important roles in acute radiation responses (Paris et al., 2001; Rotolo et al., 2008), as well as in the development of radiation fibrosis and the mechanisms of chronicity of injury (Wang et al., 2002a,b; Hauer-Jensen et al., 2004).

(468) While normal endothelial cells are relatively resistant to apoptotic death, these cells do undergo apoptosis after exposure to high radiation doses, as used in radiotherapy. The fact that endothelial cell apoptosis is ceramide dependent (Kolesnick and Fuks, 2003) has been exploited as a method to protect against injury to vascular structures and organs where endothelial injury plays a major role.

(469) After lower, more clinically relevant radiation doses, the predominant effects of radiation involve a shift in the thrombohaemorrhagic balance towards the procoagulant state (it is slightly anticoagulant under normal circumstances), increased fibroproliferative properties, and increased chemotactic and immune-cell-activating properties (Hauer-Jensen et al., 2004).

(470) Many 'endothelial-directed' approaches have been investigated in attempts to ameliorate toxicity in normal tissues (Ward et al., 1998; Wang et al., 2007a). However, traditional anticoagulants generally have the disadvantage that, when used in effective doses, they are associated with a significant risk of bleeding. Other approaches, discussed below, may partly circumvent these obstacles.

(471) One of the more promising endothelial-oriented protection strategies involves inhibition of the enzyme hydroxymethyl-glutaryl coenzyme A (HMG-CoA) reductase by statins. Statins inhibit the rate-limiting step in cholesterol synthesis but have also been shown to exhibit many lipid-independent, vasculoprotective effects. Most of these effects are mediated by increased expression and/or activity of endothelial nitric oxide synthase (eNOS).

3.2.8. Enhancers of normal tissue response

Hyperbaric oxygen

(472) Normal tissues are generally considered to be well oxygenated, and hence their radiation response would be expected to be unaffected by the supply of

additional oxygen. Nonetheless, there are examples of the sensitising effect of hyperbaric oxygen compared with normobaric oxygen on the radiation response of normal human tissues; for example, a 25–40% dose reduction is required for equivalent skin reactions, and 10% dose reduction in the case of avascular laryngeal cartilage injury. Studies of the dose dependency of these effects in various tissues in rodents showed that, in most cases, the sensitising effect was independent of dose, implying the presence of a homogeneous low level of oxygen in the target tissues (Hendry, 1979). There are no reports of such sensitisation in humans using chemical radiosensitisers. However, in rodent tissues, there are examples of such chemoradiosensitisation requiring between 10% and 30% radiation dose reduction for equivalent effects among different tissues.

Antimetabolites

(473) Strong synergy with radiotherapy has been reported for gemcitabine, which is an antimetabolite nucleoside analogue that inhibits DNA synthesis and homologous DNA repair, affects the cell cycle, modifies intracellular metabolism, and lowers the threshold for radiation-induced apoptosis. It is used as a tumour radiosensitiser, but it also acts to a lesser extent as a radiosensitiser of normal tissue responses. Intermediate synergy with radiotherapy has been reported for 5-fluorouracil and capecitabine, and weak synergy has been reported for hydroxyurea and methotrexate (reviewed in Hall and Giaccia, 2006).

Alkylating agents

(474) Alkylating agents attach an alkyl group to DNA, which crosslinks guanine nucleobases and can inhibit DNA repair and successful cell division. Some alkylating agents are active under normal cellular conditions, whereas others require activation by cytochrome p450. The latter include alkyl sulfonates, ethyleneimines and methylmelamines, nitrogen mustards, nitosoureas, triazines, imidazotetrazines, and platinum analogues. Strong synergy with radiotherapy effects in normal tissues has been noted with DTIC (Dacarbazine), intermediate synergy with platinum analogues, and weak synergy with BCNU (bis-chloroethylnitosourea) and CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitosourea) (reviewed in Hall and Giaccia, 2006).

Anti-angiogenic drugs

(475) The recent use of anti-angiogenic drugs to improve the radiation response of tumours has prompted questions about possible detrimental effects in normal tissues. Skin reactions after irradiation of subcutaneous experimental tumours receiving antivascular endothelial GF (VEGF) treatment were not increased. However, histological changes have been noted in the kidney, and further studies of late reactions in normal tissue after radiation and anti-VEGF treatments were recommended (Nieder et al., 2006).

Other agents

(476) Strong synergy with radiotherapy and increased effects in normal tissues in rodents have been reported for bleomycin (causes DNA strand breaks directly),

actinomycin D (inhibits transcription by complexing with DNA), and mitomycin C (inhibits DNA and RNA synthesis) (Von der Maase, 1986; Von der Maase et al., 1986). Strong synergy has also been noted between radiotherapy and cetuximab in the treatment of colorectal, and head and neck cancer. Cetuximab blocks epidermal growth factor receptor dimerisation and tyrosine kinase phosphorylation, which inhibits tyrosine kinase pathway signal transduction. However, epidermal growth factor receptor inhibition was not found to alter the radiation response of rodent oral mucosa to fractionated irradiation, or to interfere with mucosal repopulation processes. Weak synergy between radiotherapy and paclitaxel, which inhibits depolymerisation of tubulin in the spindle apparatus, thereby inducing apoptosis in dividing cells, has been noted (reviewed in Hall and Giaccia, 2006).

Recall reactions

(477) Radiation recall refers to inflammation and other reactions developing in previously irradiated areas that are subsequently exposed to a second agent. Radiation recall reactions have been attributed to a wide range of cytotoxic agents since they were first reported with actinomycin D. These include taxanes, anthracyclines, cytarabine, bleomycin, capecitabine, vinblastine, etoposide, methotrexate, melphalan, dacarbazine, oxaliplatin, hydroxyurea, 5-fluorouracil, and IFN. Other non-cytotoxic agents such as simvastatin, isoniazid, rifampicin, pyrazinamide, and tamoxifen have also been implicated. Approximately 70 cases of recall have been reported since the first report in 1959 (Friedlander et al., 2004; Caloglu et al., 2007). Re-irradiation of a previously irradiated area may also elicit a similar response. In this case, the mechanism is a dose-dependent incomplete recovery after the initial irradiation (Stewart, 2002).

3.2.9. Genetic and comorbidity factors

(478) Several human genetic disorders are characterised by immune dysfunction and hypersensitivity to ionising radiation. Ataxia telangiectasia (ATM), ATM-like disorder, Nijmegen breakage syndrome, severe combined immune deficiency (SCID), ligase IV syndrome, and Seckel syndrome are all disorders exhibiting very high radiosensitivity. To a lesser extent, increased radiosensitivity has been proven for xeroderma pigmentosum variant, Fanconi anaemia, human progeria syndromes, and dyskeratosis congenita. Abnormal DNA repair and cell death regulation in such individuals may result in higher vulnerability to irradiation. Some of them also manifest chromosome instability that is associated with higher incidence of cancer. Both the chromosomal instabilities and neoplastic outcomes are related to abnormalities of DNA metabolism, DNA repair, cell-cycle regulation, or control of apoptosis (Hecht and Hecht, 1990; ICRP, 1999; Bourguignon et al., 2005).

(479) The proportion of individuals in the population that have high hypersensitivity (two- to three-fold) is <1%, but there is a much higher proportion with intermediate sensitivity between these and the average (Scott, 2000). In cases of high hypersensitivity associated with homozygous gene mutation or silencing, experiments using SCID or ATM (repair-deficient) mice have shown that many

tissues are sensitised to varying degrees (Hendry and Jiang, 1994; Westphal et al., 1998).

(480) Other pathological conditions involving immune dysfunction, such as autoimmune diseases and acquired immunodeficiency syndrome (AIDS) could also be associated with higher radiosensitivity. Due to the combination of hypersensitivity to radiation and immunodeficiency, the radiation effects on the immune system may be more severe in these patients. Delayed repair of radiation-induced DNA damage and increased lymphocyte radiosensitivity have been found in patients with autoimmune diseases (systemic lupus erythematosus, juvenile rheumatoid arthritis, systemic sclerosis, and polymyositis). Patients with lymphocytes in the active phase are more radiosensitive than patients in the remissive phase of these diseases (Cossu et al., 1991).

(481) AIDS patients exhibit higher radiotoxicity. Ionising radiation activates human immunodeficiency virus-1 replication, and bystander effects involving ROS seem to be involved in this activation. The observed higher radiotoxicity may be due not only to the immune dysregulation associated with this disease, but also to decreased levels of endogenous antioxidants combined with a chronic state of oxidative stress (UNSCEAR, 2009).

3.3. Influence of modifiers on radiation response in tissues

3.3.1. Haematopoietic and immune systems

Background

(482) Patients or personnel exposed to myelosuppressive radiotherapy or potentially lethal doses of radiation consequent to a nuclear terrorist event or accident have few protective drugs approved by respective regulatory agencies. Although many drugs, HGFs, or colony stimulating factors (CSF), alone or in combination, have been evaluated in animal models, few have progressed successfully through clinical trials and been approved for treatment of radiation-induced myelosuppression in humans.

(483) Treatment strategies for personnel exposed to acute, potentially lethal doses of radiation have been the subject of several international conferences over the past 20 years. These strategies are aimed at reducing injury, and if successful, they will increase threshold doses. Although a consensus for treatment was presented in a 1993 meeting (MacVittie et al., 1996) and in guidelines for medical management of ARS (Waselenko et al., 2004), a US Food and Drug Administration (FDA)-approved protocol for the treatment of lethally irradiated personnel has not been finalised. In an effort to facilitate approval of new drugs to treat severely irradiated personnel, the FDA has published the guidelines known as the 'Animal Rule' (Crawford, 2002). This publication establishes guidelines for the gathering of evidence needed to demonstrate efficacy against the lethal effects of radiation when efficacy studies in humans cannot be conducted ethically. In these cases, the FDA will rely on well-controlled evidence from relevant, well-characterised animal models to provide substantial and consistent evidence of treatment effectiveness.

(484) There is a substantial and consistent database in small and large animal models that demonstrates the efficacy of numerous cytokines in the treatment of radiation-induced myelosuppression and mortality. Additionally, there are several studies in rodents and non-human primates that suggest the ability of cytokines such as keratinocyte growth factor (KGF) or IL-7 to stimulate immune reconstitution in prophylactic and mitigation regimens, respectively. The most important of these are described below.

(485) The translation of treatment efficacy from relevant animal models to the human condition is less consistent. The FDA has approved four cytokines for the treatment of chemotherapy-induced neutropenia and/or neutropenia consequent to myeloablative conditioning for stem cell transplantation. These are G-CSF, granulocyte-macrophage colony-stimulating factor (GM-CSF), pegylated G-CSF, and IL-11. However, regulatory approval for cytokines to treat radiation- or chemotherapy-induced immunosuppression via prophylaxis, mitigation, or therapeutics has not been forthcoming to date.

Treatment for haematopoietic ARS consequent to terrorism or accidents

(486) HGFs have been used in several cases of accidental exposures (Table 3.1). For example, in the Goiania accident in Brazil involving ^{137}Cs , the use of GM-CSF was considered to be of some benefit but it did not rescue the individuals from death, probably because of its late application (Butturini et al., 1988). Treatment strategies for personnel exposed to potentially lethal doses of radiation have been the subject of several international conferences and working groups over the past 15 years (Browne et al., 1990; MacVittie et al., 1996; Ricks et al., 2002; Waselenko et al., 2004). Based on the consensus for treatment of radiation injuries developed at the 1993 meeting (MacVittie et al., 1996), as well as recommendations from the Strategic National Stockpile Radiation Working Group (Waselenko et al., 2004), the US Centers for Disease Control and Prevention has developed a protocol entitled 'Neupogen for the treatment of ARS following a radiological incident'. In this protocol, individuals who have been exposed to radiation in the range of 3–10 Gy, and who have a diagnosis of the haematopoietic syndrome as manifest by neutropenia ($\text{ANC} \leq 500/\mu\text{l}$), would be treated with filgrastim $5 \mu\text{g}/\text{kg}/\text{day}$ subcutaneously, in combination with medical management (intravenous fluids and antibiotics). Treatment should start as soon as possible after exposure and continue until ANC is $>1000/\mu\text{l}$ for 2–3 consecutive days. Treatment beyond 21 days could be extended if ANC fails to reach $>1000/\mu\text{l}$, or if ANC, once above that threshold, drops below and remains at $<1000/\mu\text{l}$ for several days.

Treatment for haematopoietic myelosuppression

(487) The number of patients receiving whole-body radiation exposure and treatment with HGFs or cytokines is limited, and therefore the database is restricted to clinical regimens in which large-field irradiation is administered and radiation-induced myelosuppression is of a degree that HGFs would be employed. In this case, the risk management approach should dictate that the incidence of febrile

Early and Late Effects of Radiation in Normal Tissues and Organs

Table 3.1. Summary of effects of hormonal suppression on protection and stimulation of gonadal functions after cytotoxic therapies (Meistrich and Shetty, 2008).

Species	Effects of hormonal suppression in males	Effects of hormonal suppression in females
Mouse	Pretreatment suppression does not protect endogenous spermatogenesis Suppression moderately enhances spermatogenesis from transplanted spermatogonia Post-treatment suppression slightly stimulates recovery from surviving stem cells	Mixed results on protection of primordial follicles from cyclophosphamide No protection of primordial follicles from radiation
Rat	Pretreatment and post-treatment suppression markedly stimulate spermatogenic recovery from stem cells Suppression markedly enhances spermatogenesis from transplanted spermatogonia	Mixed results on maintenance of primordial follicle number during prolonged GnRH agonist treatment (independent of cytotoxic exposure) GnRH agonist, but not progestin, partially protects primordial follicles from irradiation damage
Non-human primate	Neither pretreatment nor post-treatment suppression enhance recovery of spermatogenesis after irradiation	Prolonged GnRH agonist treatment maintains primordial follicle numbers during cyclophosphamide treatment but no proof of protection against cyclophosphamide-induced damage Suppression offers no protection from radiation-induced loss of primordial follicles
Human	Suppression before and during therapy fails to protect spermatogenesis from damage by cancer chemotherapy or radiotherapy (six studies) Suppression with testosterone before and during therapy protects spermatogenesis from damage by cyclophosphamide (one study) Delayed post-treatment suppression fails to restore spermatogenesis	Several non-randomised studies (some with concurrent controls) indicate that suppression markedly protects against premature ovarian failure One small randomised study showed no protective effect of suppression

GnRH, gonadotropin-releasing hormone.

neutropenia (FN) exceeds 20% of the patient population. Three clinical studies in the early 1990s demonstrated the efficacy of G-CSF administered on the first day of irradiation and continued until patients reached a target number of circulating neutrophils (ANC). G-CSF increased white blood cells and ANC, and decreased infectious episodes and the need for antibiotics (Knox et al., 1994). A cautionary note was extended in a study using G-CSF ‘during’ large field radiotherapy, which demonstrated that the combined treatment reduced mobilisation of CD34+ cells and ‘exhausted’ the bone marrow capacity (Pape et al., 2006).

(488) The American Society of Clinical Oncology and the European Organisation for Research and Treatment of Cancer have published ‘evidence-based’ clinical

practice guidelines on the use of HGFs for chemotherapy-induced myelosuppression as a primary risk factor for infection-related morbidity and mortality, as well as dose-limiting toxicity and risk of developing Grade 3/4 FN (Aapro et al., 2006; Smith et al., 2006). The US guidelines were extended for the management of patients exposed to lethal doses of total-body radiotherapy, including the prompt use of CSF or pegylated G-CSF. The European guidelines recommend the use of G-CSF when a chemotherapy regimen is associated with FN in >20% of patients, and in general recommend the use of CSFs and pegylated G-CSF to prevent FN and FN-related complications.

(489) The impact of the use of CSFs in children and the elderly has been the focus of several meta-analyses (Sung et al., 2004, 2007; Wittman et al., 2006), as well as a European Elderly Task Force (Repetto et al., 2003). These studies show that primary prophylaxis with CSFs decreases the rate of infection, incidence of FN, and duration of severe neutropenia.

(490) The CSFs – G-CSF, GM-CSF and pegylated G-CSF – remain the only regulatory (FDA) approved drugs available for the treatment of acute radiation-induced myelosuppression after potentially lethal exposures.

Experimental data on treatment of haematopoiesis suppression

Cytokines and growth factors

(491) Cytokines and GFs can enhance haematopoietic recovery after radiation exposure. Animal studies have shown that IL-1, IL-3, IL-6, IL-11, M-CSF, G-CSF, pegylated G-CSF, G-CSF mimetic (leridistem), pegylated leridistem, GM-CSF, TNF, c-kit ligand, Flt-3 ligand, thrombopoietin, megakaryocyte growth and development factor, VEGF, and several chimeric GFs containing two ‘linked’ cytokines and a number of G-CSF peptide mimetics or G-CSF or thrombopoietin receptor agonists can stimulate haematopoiesis after irradiation (MacVittie et al., 1996). The majority of cytokines and their inducers are most effective when initiated within the first 24 h after irradiation, although cytokines such as IL-1 and TNF are also effective via prophylaxis. All of these HGFs demonstrated significant ‘potential’ for moving from ‘bench to bedside’ (i.e. for use in humans). It appeared that control of radiation- or chemotherapy-induced myelosuppression and consequent morbidity was within reach. However, the translation from preclinical efficacy in animal models to successful clinical trials has proved difficult and elusive for many HGFs, with only G-CSF, pegylated G-CSF, GM-CSF, and IL-11 currently approved for treatment of respective lineage-specific myelosuppression.

(492) Activation of the NFκB pathway induces multiple factors that contribute to cell protection and promote tissue regeneration, including apoptosis inhibitors, ROS scavengers, and cytokines. CBLB502, a polypeptide drug derived from *Salmonella flagellin*, is a Toll-like receptor 5 agonist, acting as an NFκB-inducing agent that activates tumour-specific anti-apoptotic mechanisms. A single injection of CBLB502, given before lethal TBI, inhibited pro-apoptotic pathways and protected mice from gastrointestinal and haematopoietic ARS, resulting in improved survival. CBLB502 did not alleviate radiation-induced decreases in bone marrow and blood cellularity,

but did protect HSCs and early progenitors, as judged by preservation of granulocyte/macrophage colony-forming cells and stem cell populations in the bone marrow. Additional studies in non-human primates were, however, not statistically significant (Burdelya et al., 2008). CBLB502-mediated radioprotection in mice is likely to involve multiple mechanisms, including enhanced expression of *SOD2* and induction of multiple cytokines (G-CSF, IL-6, TNF α) (Burdelya et al., 2008).

(493) The results in murine systems await confirmation in larger species such as canines or non-human primates. The success of drugs in the larger species must follow through to clinical trials or controlled studies under the FDA for approval to treat radiation-induced cellular damage in clinical protocols or lethally irradiated personnel consequent to a terrorist or accidental event.

Antioxidants

(494) The protective effects of antioxidants are mainly due to the scavenging ability of ROS (Tominaga et al., 2004; Prasad, 2005). Antioxidants such as ascorbic acid, phamitidin, melatonin, and Tempol also reduce radiation-induced apoptosis of lymphocytes (Zhou et al., 2006; Soule et al., 2007; Mozdarani and Ghoraeian, 2008). Human peripheral blood lymphocytes treated with melatonin (Shirazi et al., 2007), cyclic nitroxides (Soule et al., 2007), and other antioxidants (Jagetia et al., 2003) show a significant reduction in radiation-induced chromosomal damage in vitro. Antioxidants also activate enzymes involved in the repair of DNA lesions, and decrease the activity of NOS, a pro-oxidative enzyme (Shirazi et al., 2007). Continuing administration of a pectin-rich diet after chronic radiation exposure stimulates the phagocytic activity of blood neutrophils and monocytes, NK activity, as well as cellular and humoral immunity (Akleyev et al., 1995).

(495) Recent studies have unveiled a potential role for *FoxO* genes and their protein transcription factors as crucial HSC survival factors against oxidative stress (Tothova et al., 2007). These studies demonstrated that transgenic mice that had switched off *FoxO1*, *FoxO3*, and *FoxO4* in their haematopoietic system contained more ROS than normal cells, and that these increased ROS levels could be returned to normal by administration of antioxidants. The data also implied that *FoxO* genes are important in cell-cycle regulation, maintaining HSC quiescence, and preserving self-renewal capacity and long-term marrow repopulation, which was defective in the *FoxO*-deficient mice. The *FoxO* genes represent another target for modulating protein products that may preserve or rescue HSCs from radiation-induced oxidative stress and DNA damage. Additional studies demonstrate that the *FoxO3* transcription factor represses ROS in HSCs via regulation of the mutated *ATM* gene, and that this repression is required for maintenance of the HSC pool. Loss of *FoxO3* results in enhanced accumulation of ROS and defects in HSC function. These investigators also observed decreased expression of *ATM* and increased expression of its target p16 in the *FoxO*-deficient HSCs. The *ATM*-deficient mouse model has been used to demonstrate that elevation of ROS levels induces HSC-specific phosphorylation of p38 MAPK, which is accompanied by defective maintenance of HSC quiescence (Ito et al., 2006). Inhibition of p38 MAPK rescued defects in the repopulating ability and quiescence of HSCs.

Demonstration of the molecular mechanisms regulating HSC function and life span will be essential to developing new generation treatments for radiation effects in the haematopoietic system.

Stem cell therapy

(496) The number and quality of HSCs that survive irradiation are of critical importance for haematopoietic and immune recovery. A spontaneous recovery occurs if >2% of HSCs and precursors remain intact for replication and differentiation. Reduction in the number of HSCs below this critical value serves as a basis for administration of replacement therapy with haematopoietic cells (Flidner et al., 2002). The feasibility of haematopoietic and immune recovery via injections of autologous or allogeneic stem cells has been established in a number of laboratories using experimental animals with ARS (Chertkov, 2004).

(497) Mesenchymal stem cells (MSCs) are non-haematopoietic, multipotent progenitor cells that are able to engraft at a very low level into the bone marrow, lung, and muscles of non-irradiated animals. TBI increases engraftment of human MSCs in the brain, heart, bone marrow, and muscles, both at the site of radiation injury and outside the irradiation fields. Both human and murine MSCs are immunosuppressive, but murine MSCs lack major histocompatibility complex class II expression (Francois et al., 2006). MSCs reduce lymphocyte proliferation in mixed lymphocyte cultures. Lymphocyte proliferation induced by various mitogens is markedly reduced in the presence of autologous or allogenic MSCs. MSCs constitutively secrete a large number of cytokines, chemokines, and extracellular matrix proteins, and promote the expansion and differentiation of HSCs in vitro and in vivo. Potential uses of MSCs include stromal support for enhanced haematopoietic recovery after HSC transplantation, and the manipulation of immune responses (Le Blanc, 2003).

(498) Local irradiation of mice in addition to TBI increased homing of injected MSCs to the injured tissues and to the tissues outside the local irradiation field (Mouiseddine et al., 2007). There is evidence indicative of increased numbers of MSCs homing in tissues following a severe multi-organ injury as a result of ARS in primates (Chapel et al., 2003). The mechanism by which MSCs home to and engraft in specific tissues and migrate across site-specific endothelium remains to be defined. It is likely that irradiated (injured) tissue, such as vascular and marrow niches for HSCs or the gastrointestinal niche, express specific receptors/ligands in a gradient that facilitates attraction, adhesion, and engraftment to the injured site (Chamberlain et al., 2007). As noted above, translation to the clinic will prove difficult given that engraftment levels in adult animals are low and there are large interspecies differences.

Experimental data on treatment of immunosuppression

(499) Postirradiation immunodeficiency conditions can play a considerable role in the development of both early tissue reactions (inflammation) and long-term effects (increased risk for infectious complications, fibrosis, carcinogenesis) (UNSCEAR, 2006; Wynn, 2008). Recovery of a complete, functional immune repertoire after

moderate-to-severe radiation-induced lymphopenia requires HSC regeneration and production of early thymic progenitors and their continued seeding of a competent thymus (Bhandoola and Sambandam, 2006). As there are no effective treatments currently approved for clinical use, new strategies are required to promote thymic-dependent T-cell regeneration. The thymic micro-environment offers another target for treatment of immune suppression. The ability to enhance seeding of early thymic progenitors and/or T-cell regeneration within the niche may be of marked benefit. The thymic epithelial cells (TECs) are constantly renewing themselves while maintaining a steady-state ratio within the thymocyte subsets, and are likely to be amenable to regulation by exogenous GFs (Gray et al., 2006). The nature and extent of postradiation immunodeficiency can be modified by antioxidants, cytokines, and GFs, which can stimulate immune regeneration via effects on bone-marrow-derived HSCs and/or early thymic progenitors, as well as stimulating recovery and function within the thymic niche (Rossi et al., 2007). Several cytokines and immunomodulators such as IL-1, IL-2, IL-4, IL-7, IL-15, IL-17, c-kit ligand, Flt-3 ligand, thymic stromal lymphopoietin, bone morphogenetic proteins, and FGF are associated with T-cell survival, proliferation, differentiation, enhanced thymopoiesis, homeostatic peripheral expansion, and functional recovery of T cells. However, few of these agents have progressed to clinical trials, and therefore clinical relevance with respect to stimulated recovery of the immune system remains to be determined.

Cytokines and growth factors

(500) A successful prophylactic approach using KGF to stimulate recovery of damaged epithelium within the thymic niche has been reported in rodent studies (Min et al., 2002). KGF, a member of the acidic FGF-7 family, is produced by TECs in both the cortical and medullary regions. The KGF (FGF-7) receptor is expressed on TECs and, in turn, TECs respond to KGF and support thymocyte survival (Rossi et al., 2002). The rationale for prophylactic use of KGF is based on the fact that IL-7 is produced in situ by a subset of TECs (Chung et al., 2001). The literature documents treatment efficacy of prophylactic administration of KGF in various models of murine BMT. KGF pretreatment increased thymopoietic capacity of mice after congenic or allogenic BMT and after various conditioning regimens (6.5–14.0 Gy or cytotoxic therapy). The KGF-treated mice had an increased frequency of intrathymic cells expressing IL-7 transcripts, which suggests that the KGF-IL-7 axis is responsible for thymopoiesis following BMT and immune recovery.

(501) IL-7 is produced by a subset of TECs and bone marrow cells, and is a stimulus for proliferation, survival, and differentiation of immature thymocytes (Fry and Mackall, 2005). IL-7 treatment of irradiated mice resulted in preferential expansion of CD8+ T cells and more rapid normalisation of the CD4/CD8 ratio. Additional studies showed that mice treated with IL-7 following BMT had more rapid return of thymic cellularity, thymic cellular subsets, peripheral CD4+ cells, and improved antigen-specific T- and B-cell function (Bolotin et al., 1996). Experiments in monkeys showed that IL-7 treatment of moderately CD4+-depleted Simian immunodeficiency

virus-infected macaques increased both CD4+ and CD8+ T cells, and enhanced homeostatic peripheral expansion (Fry et al., 2003; Moniuszko et al., 2004).

(502) Flt-3 ligand, while not in clinical trials for treatment of radiation or chemotherapy-induced immunosuppression, is an essential component of in-situ physiological regulation of haematopoietic and lymphoid development, as well as a functional immune response in lymphopenic hosts. Use of Flt-3 ligand in mouse BMT models suggested that it is capable of enhancing both thymic-independent homeostasis and thymopoietic pathways for T-cell restoration (Fry et al., 2004; Kenins et al., 2008). Furthermore, Flt-3 ligand promotes dendritic cell expansion and thereby augments antigen-driven peripheral T-cell homeostasis. In fact, the recovery of dendritic cells may be a rate-limiting event in efficient homeostatic peripheral expansion.

Antioxidants

(503) Antioxidants exert a stimulating effect on innate immunity following irradiation in a wide range of doses. Glutathione and its precursors, such as cysteine and N-acetylcysteine, activate both lymphocytes and NK cells after low-dose whole-body gamma irradiation (0.5 Gy) (Kojima et al., 2002). Glutathione increases IL-2 synthesis in lymphocytes, resulting in an enhancement of NK cell proliferation and an increase in cytotoxic activity (Meydani, 1991). Metallothioneine-inducing treatment increased the relative number of neutrophils in peripheral blood, and stimulated spleen cells to increase the number of plaque-forming cells in immunised mice after lethal doses of gamma radiation (7–9 Gy) (Matsubara et al., 2000).

(504) Antioxidants injected before irradiation exerted stimulatory effects on cell-mediated immunity in rats. Dibunole administered before irradiation of rats (6 Gy) accelerated recovery of the thymic secretory function and increased the cellularity of the thymus and spleen. Dibunole also enhanced the immunostimulatory effect of T-activine (a thymic preparation) in rats after irradiation, which resulted in a reduction of blood corticosteroid (Grinevich and Martynenko, 1995). There is some evidence indicating that vegetative antioxidants (Ginsan) are able to induce proliferation of lymphokine-activated killer cells, and production of several cytokines (such as IL-1, IL-6, IFN γ , and IL-12) required for haematopoietic recovery. Ginsan was shown to enhance Th1 function while interfering with the radiation-induced Th2 response (UNSCEAR, 2009).

Other experimental approaches for stimulated immune recovery

(505) Animal studies have shown that immunisation and vaccination can significantly modify postexposure T-cell-dependent immunity changes. However, effects are variable depending on strain and type of animal, antigen, and type of response (Matsubara et al., 2000; Ina et al., 2005).

(506) Vaccines can also stimulate the phagocytic activity of neutrophils and bactericidal blood serum properties of irradiated experimental animals (Chertkov, 2004). Antitubercular and antituberculosis BCG vaccines decrease chromosomal aberrations in bone marrow cells early after irradiation (Andrushchenko et al., 1996).

(507) Microbic cell components (polysaccharides and lipopolysaccharides) can also exert postirradiation immunostimulatory effects. Enhanced proliferation and migration of HSCs, accelerated cell differentiation, and an increase in the number of haematopoietic foci in the bone marrow and spleen all result in less severe cytopenia (Andrushchenko et al., 1996). In irradiated mice, glucan (beta-1, 3-linked polysaccharide) stimulates macrophages to secrete cytokines (IL-1, TNF), inducing production of HGFs by T lymphocytes, fibroblasts, and endothelial cells. As a result, glucan was able to reduce infection significantly, and to substantially increase the regeneration of red bone marrow after irradiation (Patchen et al., 1989). Similarly, glycolipid trehalose dimycolate can increase host defence mechanisms against a variety of micro-organisms, and increase survival after TBI (Giambarresi and Walker, 1989).

3.3.2. Digestive system

(508) Our understanding of the complex pathogenetic mechanisms that lead to development of radiation-induced bowel injury has improved considerably over the last 20–30 years. Hence, extensive preclinical and clinical evaluation of pharmacological compounds, biological response modifiers, nutritional supplements, and dietary interventions as strategies to prevent radiation enteropathy has taken place. However, despite promising results at the preclinical stage with some of these interventions, very few are in general use in the clinic, as shown by several evidence-based clinical reviews (Benson et al., 2004; Rubenstein et al., 2004; Feyer et al., 2005; Maranzano et al., 2005; Keefe et al., 2007).

(509) Prophylactic interventions aimed at ameliorating normal tissue radiation injury fall into two conceptually different categories: (a) strategies that interfere with radiation-specific mechanisms of injury (e.g. antioxidants, free radical scavengers, and other cytoprotective agents); and (b) strategies that aim to modulate various pathophysiological, cellular, or molecular characteristics of the tissue to increase its radiation tolerance or enhance its repair capacity.

Antioxidants, free radical scavengers, and cytoprotective agents

(510) Preclinical gene therapy studies demonstrate that MnSOD can ameliorate radiation toxicity in the oesophagus (Epperly et al., 1999; Stickle et al., 1999). There is also some suggestion that SOD, delivered locally, may be a radioprotector in the intestine (Guo et al., 2003).

(511) The free radical scavenger amifostine protects both the small and the large intestine in preclinical studies (Ito et al., 1986; Carroll et al., 1995), and clinical studies also suggest that amifostine protects against gastrointestinal radiation toxicity (Athanasios et al., 2003; Kouvaris et al., 2003). Interestingly, topically applied amifostine protects the small intestine of rats from injury after localised irradiation (Delaney et al., 1994a), and clinical studies suggest that intrarectal instillation of amifostine, 30 min prior to irradiation of the prostate, confers protection against radiation proctitis (Ben-Josef et al., 2002; Menard et al., 2003). Larger-scale randomised trials using topical application of amifostine are clearly warranted.

(512) A number of other antioxidants, free radical scavengers, and cytoprotective compounds have been shown to modulate the intestinal radiation responses in animal models, but have not yet undergone systematic clinical investigation. Examples include the L-cysteine prodrug, ribose-cysteine, which stimulates glutathione biosynthesis (Rowe et al., 1993; Carroll et al., 1995), tirizalad and other peroxidation inhibitors (Delaney et al., 1992; Felemovicius et al., 1998; Bonsack et al., 1999), as well as vitamin A and vitamin E (Carroll et al., 1995; Felemovicius et al., 1995; Beyzadeoglu et al., 1997).

Prostaglandins

(513) Prostaglandins or other modifiers of cyclo-oxygenase activity or components of the arachidonic acid cascade have been actively pursued as intestinal radioprotectors. The exact mechanisms by which these compounds confer cytoprotection are still not fully understood. PGE₂, enprostil (a prostaglandin E₂ analogue), and misoprostol (a PGE₁ analogue) protect against intestinal radiation toxicity in animal models (Hanson and Thomas, 1983; Tomas-de la Vega et al., 1984; Keelan et al., 1992; Delaney et al., 1994b). In a small, but provocative, clinical study, misoprostol suppositories effectively reduced symptoms of acute radiation proctopathy in patients undergoing radiation therapy of prostate cancer (Khan et al., 2000).

Cytokines, growth factors, and chemokines

(514) Many preclinical studies have demonstrated that prophylactic or therapeutic modulation of cytokines or cytokine receptors can ameliorate intestinal radiation toxicity. However, clinical trials to assess cytokine modulation in terms of efficacy, toxicity, and differential protection have yet to be performed.

(515) Among the interleukins, preclinical evidence suggests a protective effect of IL-1 (Wu and Miyamoto, 1990; Hancock et al., 1991), IL-7 (Welniak et al., 2001), and IL-11 (Potten, 1995, 1996; Orazi et al., 1996). Local (intraluminal) application of IL-11 appears to be a promising approach by which systemic toxicity of this cytokine can be avoided and a protective effect on the bowel still be retained (Boerma et al., 2007).

(516) Angiogenic growth factors [e.g. acidic fibroblast growth factor (aFGF, FGF-1), basic fibroblast growth factor (bFGF, FGF-2), and VEGF] protect against acute small bowel radiation toxicity in animal models (Okunieff et al., 1998; Paris et al., 2001). While these cytokines may confer some protection, the use of angiogenic growth factors in the cancer treatment situation is problematic due to concerns regarding stimulated tumour growth.

(517) The keratinocyte growth factors, KGF-1 (FGF-7) and KGF-2 (FGF-10), have been investigated as potential radioprotectors. KGF-1 clearly ameliorates acute intestinal radiation toxicity in animal models (Khan et al., 1997; Farrell et al., 1998). Most of the beneficial effects of the KGFs are probably related to their epithelial growth-promoting activities. In contrast to aFGF and bFGF, which activate several

FGF receptors, KGF mainly activates the receptor FGFR2IIIb on epithelial cells, and therefore may have greater target cell specificity.

(518) Transforming growth factor beta-1 (TGF- β 1) has been the subject of particularly intense investigation because of its fibrogenic properties. Numerous clinical and animal studies have provided strong correlative evidence supporting a role for TGF- β 1 in radiation fibrosis in many organs, including the intestine. A preclinical study demonstrated a direct mechanistic role for TGF- β 1 in intestinal radiation fibrosis, as well as the potential for anti-TGF- β 1 strategies to ameliorate delayed radiation enteropathy (Zheng et al., 2000b). Substantial efforts are currently devoted to development of small molecule inhibitors of TGF- β and TGF- β signalling (Boerma et al., 2008b).

(519) Evidence from preclinical studies suggests that other cytokines may be considered as intestinal radiation response modifiers. Hence, stem cell factor, mast cell growth factor, c-Kit ligand, GH, insulin-like growth factor-1 (IGF-1), and certain chemokines (cytokines with the ability to induce directed migration of cells, such as inflammatory cells, to sites of tissue injury) also have the ability to protect the intestine against acute radiation injury (Leigh et al., 1995; Howarth et al., 1997; Silver et al., 1999; Vazquez et al., 1999; Arango et al., 2001). The potential of these mediators as modifiers of the intestinal radiation response in the clinical situation is still unknown.

Enterotrophic strategies

(520) There has been long-standing interest in the use of enterotrophic strategies (i.e. interventions that promote growth of the intestinal mucosa) to reduce intestinal radiation toxicity. The purpose of such interventions is to increase the resistance of the intestinal mucosa to radiation injury and/or enhance its capacity for recovery after radiation exposure. Enterotrophic strategies with the potential to protect the intestine from radiation injury include some cytokines, gastrointestinal peptide hormones, and a variety of nutrients.

(521) Elemental diets are enteroprotective in animal studies, but results from clinical trials are mixed (Douglass et al., 1978; Brown et al., 1980; Foster et al., 1980; McArdle et al., 1986; Craighead and Young, 1998). There was substantial interest in elemental diets for intestinal radioprotection in the 1970s and 1980s, but this interest has now waned due to cost, logistics, compliance issues, and questionable clinical benefits.

(522) Several different nutrients, such as fibre, short-chain fatty acids, and the amino acids glutamine and arginine, enhance growth of the intestinal mucosa and ameliorate small bowel radiation toxicity in preclinical and, in some cases, clinical studies. Of these, the semi-essential amino acid, glutamine, has received the most attention. Glutamine was found to support mucosal structure and recovery, and ameliorate intestinal radiation toxicity in some preclinical studies (Klimberg et al., 1990; Campos et al., 1996), although not in others (McArdle, 1994; Hwang et al., 2003). However, a large clinical randomised trial showed that glutamine had no effect on acute intestinal toxicity in patients undergoing pelvic radiation therapy (Kozelsky et al., 2003).

(523) Numerous gastrointestinal peptide hormones have potent enterotrophic activities. This category includes GH, neurotensin, cholecystokinin, bombesin, and peptide YY. While these peptides have protective effects in various types of intestinal injury, they have not yet been subjected to systematic testing in radiation injury. The enterotrophic peptide hormone, glucagon-like peptide-2 (GLP-2) and synthetic analogues are currently being investigated as enteroprotective interventions. Preclinical results with GLP-2 in radiation enteropathy, albeit in a single-dose radiation model, appear encouraging (Booth et al., 2004; Torres et al., 2007), particularly when administration occurs before irradiation.

Anti-inflammatory strategies

(524) Although the common use of the term ‘radiation enteritis’ implies an aspect of inflammation, the use of traditional anti-inflammatory drugs to ameliorate radiation enteropathy has been generally disappointing. Acetylsalicylic acid (aspirin), an anti-inflammatory agent with antiplatelet properties, may be of some benefit in intestinal radiation toxicity (Mennie et al., 1975), whereas other NSAIDs are clearly not protective (Stryker et al., 1979). Sulfasalazine may be moderately effective in reducing acute radiation-induced intestinal side-effects (Kilic et al., 2000). Interestingly, salicylic acid derivatives developed specifically for treatment of inflammatory bowel disease are not only ineffective but possibly even harmful when used in the prophylaxis of acute intestinal radiation toxicity (Freund et al., 1987; Baughan et al., 1993; Martenson et al., 1996; Resbeut et al., 1997). Given topically as enemas, these compounds also have no effect on chronic radiation proctitis (Baum et al., 1989). The immunomodulator orazipone, on the other hand, did reduce intestinal radiation injury after localised irradiation in a rat model, although the exact mechanism by which this broad-based locally acting immunomodulator ameliorates radiation enteropathy remains to be elucidated (Boerma et al., 2006). It is possible that future agents, targeted at specific aspects of the inflammatory process, may prove more effective in modifying the intestinal radiation response.

Modulation of intraluminal contents

(525) Modification of various intraluminal factors, notably bacteria, bile, and pancreatic secretions, has been explored for many years as a strategy to ameliorate intestinal radiation injury. Combined evidence from studies involving irradiation of germ-free animals, ‘decontamination’ of animals with different antimicrobial agents, and probiotic therapies suggest that maintaining a balanced bacterial flora, rather than attempting to maximally reduce bacterial content, may be the optimal approach to minimise bowel toxicity (Salminen et al., 1988).

(526) Of the various intraluminal factors, pancreatic enzymes exert the most pronounced influence on acute intestinal radiation toxicity. Reducing pancreatic enzyme secretion in animals by surgical or dietary methods attenuates acute mucosal injury, as well as subsequent development of intestinal fibrosis (Sokol et al., 1967; Morgenstern et al., 1970; Rachootin et al., 1972; Hauer-Jensen et al., 1985). Moreover, preclinical studies show that reducing intraluminal pancreatic

secretions with a synthetic somatostatin receptor analogue, octreotide, markedly ameliorates both early and delayed radiation enteropathy (Wang et al., 1999, 2001). Octreotide is exceptionally well tolerated clinically and, because of its potent inhibitory effects on gastrointestinal secretion and motility, it is used in patients with intractable diarrhoea after cancer chemotherapy and has documented effect in patients undergoing radiation therapy (Yavuz et al., 2002). Importantly, octreotide has intrinsic antitumour and anti-angiogenic effects (Weckbecker et al., 1992a,b, 1994; Patel et al., 1994), so there is little or no concern about potential tumour protection. Hence, while the protective effects of octreotide are likely confined to the small intestine, this compound is a particularly promising candidate for intestinal radioprotection in the clinic.

Modulation of endothelial dysfunction

(527) Administration of traditional anticoagulant agents, such as heparin, warfarin, or acetylsalicylic acid, confers some, albeit inconsistent, protection against radiation injury in certain organs, including the intestine. Recent preclinical studies show that inhibition of ADP-induced platelet aggregation or direct inhibition of thrombin reduces acute and chronic intestinal radiation injury in rats (Wang et al., 2002a, 2004). Strategies aimed at restoring local endothelial anticoagulant properties, temporarily replacing the ‘natural anticoagulant’, activated protein C, or only blocking the effects of thrombin that are mediated through its cellular receptor, proteinase-activated receptor 1, are under investigation.

(528) There is strong evidence supporting the use of statins to reduce the incidence and/or severity of radiation enteropathy. Preclinical studies performed in two different laboratories have shown that statins ameliorate delayed radiation enteropathy and, albeit to a lesser extent, the acute intestinal radiation response (Haydont et al., 2007; Wang et al., 2007b). Moreover, a clinical study revealed that statin use is associated with reduced rectal toxicity in conjunction with pelvic radiation therapy (Irwin et al., 2006). It is possible that other compounds that reduce the activity of HMG-CoA reductase by other mechanisms (e.g. the vitamin E analogue, γ -tocotrienol) can further enhance the efficacy of statins as effective radiation response modifiers.

Neuro-immunomodulation

(529) Interactions between the enteric nervous system and various cell types in the intestinal wall regulate radiation-induced inflammation and fibrosis development in the gut. The sensory (afferent) nerves of the intestine appear to be particularly important in terms of these neuro-immune interactions. Sensory nerves were previously thought of solely as conveyors of stimuli from the periphery to the CNS or peripheral neural circuitry. However, it is now well established that sensory nerves also exert important local effector functions in many organs, particularly the intestine. Through interactions with epithelial cells and immune cells, notably mast cells, sensory nerves are involved in maintaining the integrity of the intestinal mucosa and in mounting an appropriate response to injury. Clinical and animal studies implicate

substance P, released by sensory nerves, in the intestinal radiation response (Christensen and Haley, 1968; Esposito et al., 1996; Forsgren et al., 2000; Hockerfelt et al., 2000), and administration of neurokinin-1 receptor antagonists ameliorates some aspects of gastrointestinal radiation toxicity (Alfieri and Gardner, 1998; Esposito et al., 1998). Work using genetically altered animal models and pharmacological response modifiers has shown that mast cells and sensory nerves have a protective effect against acute intestinal injury, and that the two major neuropeptides released by sensory nerves have opposing effects, in that substance P exacerbates, while calcitonin gene-related peptide ameliorates, the intestinal radiation response (Zheng et al., 2000a; Wang et al., 2006a,b).

Pre-exposure countermeasures for radiation accidents or radiation terrorism

(530) Pre-exposure countermeasures (radioprophylactic or radioprotective countermeasures) are interventions that either enhance the resistance and/or tolerance of normal tissues to radiation, or interfere directly with the initial radiochemical events. Such countermeasures are a priority for military personnel, first responders, and rescue and clean-up workers. There is considerable overlap between the approaches discussed above and the development of medical countermeasures for the radiation accident or terrorism scenario. The following discussion focuses on compounds that have shown particular promise in ameliorating intestinal injury after whole-body radiation exposure. The pre-exposure countermeasures that have been shown to influence the level of intestinal radiation toxicity include antioxidants, free radical scavengers, and cytoprotectors on one hand, and enterotrophic strategies on the other.

(531) Among the nutritional antioxidants, there has been strong interest in the use of vitamin A (Beyzadeoglu et al., 1997) and vitamin E (tocols) (Empey et al., 1992; Felemovicius et al., 1995; Kumar et al., 2002a). Tocols have been subject to particular interest because of their potent properties as radiation protectors. The eight naturally occurring tocopherols (α , β , γ , and δ tocopherols; α , β , γ , and δ tocotrienols) have different antioxidant properties, as well as different affinities to endothelial cells and different abilities to inhibit the enzyme hydroxyl-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. The most promising tocol compounds at the present time are γ -tocotrienol (GT3) and δ -tocotrienol, both of which show substantial activity as HMG-CoA reductase inhibitors (Kumar et al., 2009). GT3 gives a protection factor of approximately 1.3, protecting against haematopoietic and intestinal radiation injury, as well as vascular radiation injury. The combination of GT3 with the phosphodiesterase inhibitor, pentoxifylline, and/or with other classes of HMG-CoA reductase inhibitors that exert efficacy against radiation enteropathy in preclinical and clinical studies is also being investigated.

(532) Several small molecule compounds that mimic the effects of SOD and/or catalase are under development as radioprotectors, and have shown promise as countermeasures, but their ability to specifically protect from intestinal radiation lethality after TBI remains to be determined (Kumar et al., 1988; Rong et al., 1999; Vujaskovic et al., 2002a).

(533) Other antioxidant compounds that have been tested include probucol, an antioxidant that inhibits the formation of peroxides and confers intestinal protection in rats when given either intraluminally or systemically (Bonsack et al., 1999). Melatonin reduces lethality after TBI and protects against radiation-induced intestinal injury, possibly due to its radical scavenging properties, stimulatory effects on antioxidant enzymes, and enhancement of the cellular DNA repair machinery (Vijayalaxmi et al., 1999; Monobe et al., 2005).

(534) Many studies have assessed modification of cyclo-oxygenase activity or components of the arachidonic acid cascade in the context of radiation responses in normal tissues, including intestine. Inhibition of cyclo-oxygenase-2 protects against intestinal radiation injury in animal studies (Keskek et al., 2006), as do PGE and its synthetic analogues, and PGE₂ (Hanson and Thomas, 1983; Tomas-de la Vega et al., 1984). Oral administration of enprostil (a PGE₂ analogue) or luminal application of misoprostol (a PGE₁ analogue) also protects against intestinal radiation toxicity (Keelan et al., 1992; Delaney et al., 1994b). Misoprostol and a prostacyclin analogue (iloprost) were toxic when given separately, but a combination of the two compounds conferred synergistic radiation protection with considerable amelioration of toxicity (Kumar et al., 1997).

(535) Several GFs and chemokines have been shown to reduce intestinal injury after TBI. For example, IL-1 α , IL-1 β , teduglutide, TGF- β 3, IL-11, and genistein confer some radioprotection of mouse intestine (Wu and Miyamoto, 1990; Hancock et al., 1991; Potten, 1995; Potten et al., 1997). IL-7, which plays critical roles in the development of B and T cells and also influences the function of mature NK cells and monocytes/macrophages, protects intra-epithelial lymphocytes from undergoing apoptosis (Yada et al., 2001). It may also protect the intestinal stem cell compartment from radiation (Welniak et al., 2001). IL-15, a cytokine that is widely expressed by epithelial cells, stromal cells, and immune cells, promotes survival of intra-epithelial lymphocytes, inhibits expression of IL-8 and monocyte chemo-attractant protein 1 (Lai et al., 1999; Luger et al., 1999), and stimulates epithelial cell proliferation (Reinecker et al., 1996). While IL-15 has not been studied systematically in radiation injury, it confers an impressive degree of protection against the intestinal toxicity of irinotecan (CPT-11), a chemotherapeutic agent that is notorious for causing gastrointestinal toxicity, mainly due to dose-limiting diarrhoea (Cao et al., 1998).

(536) The angiogenic growth factors, aFGF, bFGF, and VEGF, are all radioprotective in the small intestine of mice exposed to TBI (Okunieff et al., 1998; Paris et al., 2001). The mechanisms of protection, however, are unclear. The many documented effects of bFGF include protection of endothelial cells from apoptosis, enhanced repair of DNA damage, and increased proliferation and enhanced restitution of intestinal epithelium. It remains to be determined whether the enteroprotective effect of bFGF is primarily a direct effect on epithelial cells (Houchen et al., 1999), secondary to reduced endothelial cell apoptosis (Paris et al., 2001), or a combination of the two.

(537) Direct enterotrophic growth factors, for example irradiation recombinant human KGF1, administered to mice before TBI or abdominal irradiation increased crypt survival and LD₅₀ (Khan et al., 1997; Farrell et al., 1998).

Postexposure countermeasures against intestinal radiation injury

(538) Postexposure countermeasures interfere with downstream events by preventing or reducing the progression of radiation toxicity and/or facilitating the eventual resolution of, or recovery from, radiation injury. For civilian accident or mass casualty situations, agents are needed that are effective when administered hours to days after radiation exposure. Compared with the plethora of compounds that exhibit robust protection of the intestine when applied before irradiation, the list of countermeasures with activity after radiation exposure is considerably shorter.

(539) Modifications of the intraluminal contents, particularly bacteria and pancreatic enzymes, have been explored as strategies to ameliorate intestinal radiation toxicity in the postexposure situation. Treatment of animals with antibiotics against the aerobic gut flora after irradiation increases survival (Mastromarino and Wilson, 1976a,b). In contrast, antimicrobials that reduce the anaerobic flora may be detrimental in the TBI situation and should be avoided. Careful selection of the antibiotic treatment regimen has been shown to protect lethally irradiated canines (Kumar et al., 2002b). A combination of oral and parenteral antibiotics may reduce bacterial translocation and confer considerable protection. In the clinical situation, it is likely that proper balance in the bacterial flora is the most important issue in terms of minimising radiation toxicity. There is also interest in probiotic therapies as a way to enhance the resistance of the gut to irradiation and/or to minimise intestinal radiation toxicity (Salminen et al., 1988; Urbancsek et al., 2001).

(540) The latency period before radiation-induced ulcers led to rectal obstruction in rats following a $LD_{90/200\text{ day}}$ dose of 23 Gy to the descending colon was much increased by use of a low-molecular-weight synthetic diet or a herbal laxative continuously after irradiation (Trott et al., 1986). The influence of tetrachlorodecaoxide (TCDO, an agent proposed to stimulate regeneration) on the chronic radiation damage was also examined when given at different times and in different amounts after irradiation (Breiter et al., 1989; Sassy et al., 1991). TCDO treatment before the acute reaction period resulted in an extension of the latency period. When TCDO was given at the highest amount used at the onset of the chronic phase, there was an increase in the survival rate. There were demonstrable signs of improved healing of the mucosa, assayed endoscopically and histologically. These studies showed the potential of special diets and promising agents given after irradiation in delaying and improving the signs of late large bowel injury.

(541) A series of dog studies from the late 1960s and early 1970s demonstrated that reducing the intraluminal content of pancreatic enzymes reduced lethality after abdominal irradiation (Morgenstern and Hiatt, 1967; Sokol et al., 1967; Morgenstern et al., 1970; Rachootin et al., 1972). The most promising approach to reduce intraluminal pancreatic secretions in humans may be by administration of synthetic somatostatin receptor analogues. Somatostatin analogues are 'universal gastrointestinal inhibitors' and are used clinically for a wide variety of gastroenterological indications. Due to their strong inhibitory effect on secretion, somatostatin analogues result in a 'pharmacological, reversible exocrine pancreatectomy'. Somatostatin

analogues are extremely well tolerated, and the maximal tolerated dose in humans has not been reached. Based on the promising preclinical and clinical results with the somatostatin analogue octreotide as a modifier of intestinal injury after localised irradiation, there is also interest in developing somatostatin analogues for use as countermeasures (Fu et al., 2009).

(542) The polypeptide compound CBLB502, derived from *Salmonella flagellin*, binds to Toll-like receptor 5 to activate signalling by NF κ B. Activation of NF κ B affects p53 and induces cytoprotective cytokines and other factors, inhibitors of apoptosis, and free radical scavenging factors. CBLB502 has been reported to confer protection against both intestinal and haematopoietic lethality after TBI in mice and non-human primates. CBLB502 improves survival when injected up to 24 h before radiation exposure, as well as when injected up to 1 h after radiation exposure (Burdelya et al., 2008).

(543) IL-11, in addition to its haematopoietic and immunomodulating activities, also serves to protect and restore the gastrointestinal mucosa. Administration of IL-11 protects mice against the intestinal effects of TBI (Potten, 1995, 1996; Orazi et al., 1996). Despite these encouraging preclinical results, systemic administration of IL-11 to humans is hampered by severe side-effects, including fluid retention and multisystem organ failure. In contrast, oral delivery of an enteric-coated formulation of recombinant human IL-11 (rhIL-11) avoids systemic uptake and is thus not associated with the toxicity seen after systemic administration (Tseng et al., 2000; Cotreau et al., 2004). A recent study showed significant protection against early intestinal radiation injury when human recombinant IL-11 was administered once daily directly into the intestinal lumen of rats (Boerma et al., 2007), suggesting that oral administration of an enterosoluble form of IL-11 may also be a promising radiation countermeasure.

3.3.3. Reproductive system

(544) Modification of the response of the reproductive system in animals has been investigated using hormonal manipulation, antioxidants, and radical scavengers, but only hormonal manipulation has been investigated in humans.

Male reproductive system

Cell signalling and hormonal manipulation

(545) Suppression of gonadotropins with medroxyprogesterone acetate during chemotherapy combined with radiotherapy did not improve the recovery of sperm counts or normalise FSH levels, which was used as a surrogate for sperm count in patients in whom sperm counts were unavailable; indeed, they appeared to be lower in the patients receiving concurrent treatment with hormonal suppression than in controls (Fossa et al., 1988). A GnRH agonist plus an anti-androgen (cyproterone acetate) was used prior to and for the duration of radiation therapy where the gonadal dose of radiation was 0.2 Gy, which allowed spontaneous recovery of sperm counts in all the control patients within 2 years (Brennemann et al., 1994). The one attempt to restore spermatogenesis by steroid hormonal suppression after

cytotoxic therapy was also unsuccessful (Thomson et al., 2002). Seven men with azoospermia secondary to high-dose chemotherapy and/or radiation therapy for leukaemia or lymphoma in childhood were treated with medroxyprogesterone acetate combined with testosterone to suppress gonadotropin and likely intratesticular testosterone levels many years after the anticancer treatment. None of the men recovered any sperm production during the 24-week follow-up after the end of hormonal treatment.

(546) The use of hormonal suppression for fertility preservation in males receiving radiation and other cytotoxic therapies has been reviewed (Table 3.1) (Meistrich and Shetty, 2008). It was shown that suppression of gonadotropin and intratesticular testosterone levels, using testosterone prior to or during exposure of rats to radiation, enhanced the subsequent recovery of spermatogenesis (Schlappack et al., 1988). Enhanced recovery was also found using oestradiol or a GnRH antagonist after 6 Gy (Shetty et al., 2004). However, no enhanced recovery was found by using oestrogen in irradiated rats (Morris et al., 1988). One group reported that a GnRH agonist shortened the time to recovery of spermatogenesis after irradiation of dogs (Nseyo et al., 1985). However, there was no stimulation of recovery of spermatogenesis in macaques by using GnRH antagonist treatment after irradiation (Kamischke et al., 2003; Boekelheide et al., 2005). Meistrich et al. (2000) proposed that prevention of the pronounced block in differentiation of surviving stem spermatogonia in rat testes after exposure to cytotoxic agents was the mechanism by which hormonal suppression appeared to protect spermatogenesis from toxicant exposure, but this is species specific. In rats, radiation produced a prolonged block to spermatogonial differentiation (Meistrich et al., 1999).

(547) Control rats and rats treated with testosterone plus oestradiol were irradiated with 0.7–2.7 Gy of high-energy neutrons (Wilson et al., 1999). The recovery of spermatogenesis was assessed 9 weeks after irradiation by testis weight, sperm count, and tubule repopulation indices. Greater recovery of spermatogenesis was observed for all endpoints, with a DMF of approximately 2 for rats treated with testosterone plus oestradiol compared with the irradiated, cholesterol-treated rats. The DMF values were similar for both neutrons and gamma rays (Kurdoglu et al., 1994), indicating that oxygen, thiols, and repair of DNA damage were unlikely to be involved in the protective effect of the hormone treatment.

(548) Sphingosine 1-phosphate (S1P) inhibits activation of caspases that are involved in apoptosis after cell injury, and hence may protect against radiation-induced injury. Intratesticular injections of S1P given 1–2 h before irradiation (0.5 Gy) did not protect against short-term germ cell loss in mice as measured by in-situ end-labelling of DNA fragmentation 16 h after irradiation (Otala et al., 2004). However, after 21 days, the numbers of primary spermatocytes and spermatogonia at G₂ were higher in the S1P-treated testes compared with the vehicle-treated testes, indicating protection of early spermatogonia by S1P, whereas the spermatid populations were similar. The authors concluded that S1P appeared to partially protect (16–47%) testicular germ cells against radiation-induced cell death.

Antioxidants

(549) The capacity of vitamin A dissolved in soybean oil to protect against spermatogonial cell killing caused by internal radionuclides was investigated in mice (Harapanhalli et al., 1994). The radiochemicals examined were DNA-binding ^{125}IdU , $\text{H}^{125}\text{IPDM}$, and the alpha-particle emitter ^{210}Po citrate. Soybean oil itself provided substantial and equal protection against the Auger effect of ^{125}IdU (DNA binding and comparable to a high-LET radiation effect), as well as against the low-LET effects of cytoplasmically localised $\text{H}^{125}\text{IPDM}$. The DMFs were 3.6 ± 0.9 and 3.4 ± 0.9 , respectively. The protection afforded by the oil against the effects of 5.3-MeV alpha particles emitted by ^{210}Po was also significant (DMF = 2.2 ± 0.4). The presence of vitamin A in the oil further enhanced the radioprotection against the effect of ^{125}IdU (DMF = 4.8 ± 1.3) and $\text{H}^{125}\text{IPDM}$ (DMF = 5.1 ± 0.6); however, no enhancement against the effects of alpha particles was seen. The authors concluded that the mechanism by which DNA-bound Auger emitters impart biological damage is primarily indirect in nature.

(550) RP-1, a herbal preparation of *Podophyllum hexandrum*, already reported to provide protection against whole-body lethal gamma irradiation (10 Gy), was studied regarding radioprotection of spermatogenesis in mice (Samanta and Goel, 2002; Samanta et al., 2004). Administration of RP-1, 2 h before irradiation, rendered a significant increase in the testis weight, repopulating tubules, resting primary spermatocytes, stem cell survival index, sperm count, and reduction in abnormalities of sperm morphology at 10, 35, and 70 days after irradiation. The thiol content of the testes was found to be increased in both the RP-1-alone group and the RP-1-pretreated 10-Gy-irradiated group compared with the 10-Gy-alone group at 8, 16, and 24 h. Irradiation (10 Gy) significantly decreased glutathione peroxidase, S-transferase, and reductase activity in comparison with untreated controls, but RP-1 treatment before irradiation countered the radiation-induced decrease in these enzyme activities. Radiation-induced lipid peroxidation was also found to be reduced at all time intervals by RP-1 pretreatment. Compared with the 10-Gy-alone group, the total protein content in testicular tissue was increased in the RP-1-pretreated irradiated group at 4 and 16 h. The authors concluded that RP-1 offered radioprotection at the biochemical and cytogenetic level by protecting antioxidant enzymes, reducing lipid peroxidation, and increasing thiol content.

Radical scavengers

(551) The radioprotection of testicular cells using amifostine and doses of radiation extending down to <1 Gy was investigated in mice (Meistrich et al., 1984). Survival of stem spermatogonia after single doses of radiation was measured by counts of repopulating tubules and by sperm head counts, with consistent results obtained for both endpoints. Protection factors obtained by injection of WR-2721 400 mg/kg 15 min prior to irradiation decreased from approximately 1.4 at radiation doses of >10 Gy to 1.0 at 2 Gy. Similarly, the radioprotection by WR-2721 300 mg/kg was reduced from a protection factor of approximately 1.35 when

the drug was given prior to a single high dose of radiation, to 1.0–1.1 when the drug was given prior to each of five daily fractions of 2 Gy. Thus, less protection of testicular stem cells by WR-2721 was observed at lower doses of radiation. This lowered protection was presumed to be due, at least in part, to a direct cytotoxic effect of WR-2721 on testicular stem cells. Protection of differentiated spermatogonia was observed with WR-2721 400 mg/kg; the protection factor was 1.4 at 1 Gy and decreased at lower doses. The protection of testicular function by WR-2721, as assayed by the return of fertility and the maximum recovered level of sperm production, was compared with the protection of stem cell survival. At 8 Gy, the protection factor of WR-2721 400 mg/kg for both functional endpoints was approximately 1.5, which was not significantly different from the value of 1.3 obtained using the stem cell assays.

(552) The radioprotective effect of various agents against dominant lethal mutations (DLM) in post-spermatogonial stages, and reciprocal translocations (RT) in spermatogonia were investigated in mice (Pomerantseva and Ramaija, 1984). Cystaphos, a combination including cystamine and 5-MOT, was most effective against DLM, and cystaphos, gammaphos and cystamine combined with 5-MOT were effective against RT. The degree of radioprotection was, however, relatively low. The efficacy of cystamine in protecting against reciprocal translocation was higher with exposure of gonocytes of 18.5-day embryos than spermatogonia of pubertal animals. The radioprotective effect varied depending on the stage of spermatogenesis, and, in all cases, it was lower than that observed in studies of protection against lethal effects of ionising radiation.

(553) Dimethyl sulfoxide (DMSO) was studied for its capacity to protect against the biological effects of chronic irradiation from incorporated radionuclides in mice (Goddu et al., 1996). DMSO was injected intratesticularly 4 h prior to a similar injection of the radiochemical, and spermhead survival was determined. ^{125}I was localised in either the cytoplasm ($\text{H}^{125}\text{IPDM}$) or the DNA ($^{125}\text{IUdR}$) of the testicular cells. Protection was observed against the high-LET-type effects of DNA-bound ^{125}I as well as the low-LET effects of cytoplasmically localised ^{125}I , with DMFs of 3.1 ± 1.0 and 4.4 ± 1.0 , respectively. No protection (DMF = 1.1 ± 0.1) was observed against the effects of high-LET 5.3-MeV alpha particles from ^{210}Po . The authors concluded that these findings provided supporting evidence that the mechanism responsible for the extreme biological damage caused by DNA-bound Auger emitters is largely radical mediated and therefore indirect in nature.

(554) The radioprotective action of a preparation from *Hippophae rhamnoides* berries RH-3, already reported to render >80% survival against whole-body 10-Gy gamma irradiation, was further investigated with respect to the testicular system (Goel et al., 2006). RH-3 was administered to mice 30 min before gamma irradiation (5 and 10 Gy), and histological parameters were assessed on the 35th day. RH-3 administration partially countered radiation-induced reduction in testis weight, sperm count, repopulation index, and stem cell survival index, and had no effect in controls. The increased frequency of abnormal sperm ($15 \pm 1\%$) caused by irradiation (5 Gy) was also reduced to $8 \pm 1\%$ by the use

of RH-3. The authors suggested that the presence of polyphenolic flavonoids and tannins in the extract and the radical scavenging activity may be responsible for the radioprotective action of RH-3.

Female reproductive system

Hormonal manipulation

(555) A review of the literature concluded that protection of primordial follicles from damage by cytotoxic agents, using GnRH analogues, had been seen in several species (Meistrich and Shetty, 2008). The protection could not involve the induction of quiescence because the primordial follicles are already dormant, but it may involve direct effects of GnRH analogues or indirect effects of gonadotropin suppression on the whole ovary. Although numerous studies in female patients undergoing chemotherapy (and some radiotherapy) indicate that GnRH analogues may be protective of ovarian function, none of the studies was prospectively randomised and thus the results are inconclusive.

(556) Radiation kills primordial ovarian follicles in all mammals studied, but those of the mouse are exquisitely sensitive and those of the rat are moderately sensitive (Baker, 1978). In mice, gonadotropin reduction due to a hypogonadal mutation or GnRH antagonist treatment failed to protect primordial ovarian follicles from radiation (Gosden et al., 1997). Treatment with a GnRH agonist, but not with medroxyprogesterone acetate, partially protected against radiation-induced loss of primordial follicles in rats (Jarrell et al., 1987, 1989). No protection from radiation-induced loss of primordial ovarian follicles in monkeys was observed with GnRH agonist treatment (Ataya et al., 1995).

(557) The use of S1P to protect against radiation-induced oocyte apoptosis has also been studied. Young adult female mice were given a single injection of S1P into the bursal cavity, which surrounds each ovary (Morita et al., 2000). Two hours later, they were irradiated with 0.1 Gy which destroyed the majority of the primordial oocyte reserve. Two weeks later, no differences were observed between mice that had not been irradiated and those that had been protected by S1P *in vivo* before irradiation. In contrast, irradiated mice that did not receive S1P suffered a pronounced loss of oocytes and reduced embryonic developmental potential of the remaining oocytes. Subsequently, it was demonstrated that S1P-based protection of the female germ line from radiation is not associated with discernible propagation of genomic damage at the anatomical, histological, biochemical, or cytogenetic level (Paris et al., 2002). Whether similar effects would be seen in the much more radioresistant human oocytes is unknown.

Radical scavengers

(558) Three-week-old female mice, with or without pretreatment with amifostine, were irradiated with 6.4-Gy gamma rays (Yoon et al., 2005). The incidence of follicular degeneration increased in ovarian follicles in the gamma-irradiated mice compared with that of the control or amifostine-treated group. There was an increase in p53 and Bax protein, and a decrease in the inactive form of caspase-3 and PARP (poly ADP ribose polymerase) protein, which cleaved into active peptides during

apoptosis. In the amifostine treatment group before irradiation, the increased rate of p53 and Bax was suppressed. The relationship between PARP and caspase-3 levels showed the protective effect of amifostine treatment before irradiation. Hence, amifostine had an inhibitory effect on ovarian programmed cell death induced by gamma rays, affecting the expression of apoptotic signalling molecules and the level of proliferation of the granulosa cells.

(559) There was also an early report of protection of ovarian follicles in mice by 2-mercaptopropionylglycine (Kumar and Uma Devi, 1983).

3.3.4. Skin

Anti-inflammatory agents

(560) Topical application of prednisolone and neomycin reduced the area of moist desquamation in cancer patients receiving single radiation doses to the skin (Halnan, 1962). A recent review concluded that corticosteroids and NSAIDs are of value in the pre-fibrotic phase and in reducing the acute inflammation associated with fibrosis; the value of these drugs when given during treatment to prevent acute or late complications remains unproven (Delanian and Lefaix, 2007). In animal systems, delays in the appearance of early radiation-induced skin reactions have been reported in mice using cortisone, in rabbits using betamethasone, and in monkeys using dexamethasone. The NSAID trimetazidine, when given with flurbiprofen, reduced moist desquamation after irradiation in rabbit skin, but not when given alone (Lefaix et al., 1992).

Superoxide dismutase

(561) Liposomal SOD was reported to reduce established radiotherapy-induced fibrosis (Delanian et al., 1994). This was also found using topical peg-SOD (polyethylene glycol) with superficial breast radiation-induced fibrosis (Benyahia et al., 1996; Campana et al., 2004). Such effects have also been observed in animal systems (Lefaix et al., 1996; reviewed by Delanian and Lefaix, 2007). However, as yet, SOD and its various preparations are not available for general clinical use.

Pentoxifylline

(562) Pentoxifylline has been reported to significantly accelerate healing of radiotherapy-induced soft tissue necrosis in mice (Dion et al., 1989). Also, in a phase II trial, there was complete restoration of refractory mandibular osteoradionecrosis by prolonged treatment with a pentoxifylline-tocopherol-clodronate combination (Delanian et al., 2011). In animals, pentoxifylline was not found to modify the early reactions when given after irradiation of mouse foot skin (Dion et al., 1989), or the early or late skin reactions in rats (Koh et al., 1995). However, it did reduce late fibrotic scars in irradiated pig skin (Lefaix et al., 1999).

α -Tocopherol (vitamin E)

(563) In a randomised trial of breast cancer patients with skin fibrosis, regression of the fibrotic lesions was observed after administration of pentoxifylline/tocopherol

(Delanian et al., 2003). However, these results were not confirmed in larger trials in breast cancer patients (Gothard et al., 2004) and patients after pelvic radiotherapy (Gothard et al., 2005). Tocopherol in combination with pentoxifylline was effective in softening and shrinking fibrotic scars developing in pig skin after high single radiation doses (Delanian, 1998; Lefaix et al., 1999), but there was no beneficial effect of tocopherol on its own in rabbits (Lefaix et al., 1992). Pig skin was also used as a model to study the effectiveness of topical application of two creams after irradiation – lipochromin (containing β carotene, tocopherol, fatty acids) and levosinum (containing methyluracil, sulfadimethoxin) – in modifying the development of both early and late radiation ($^{90}\text{Sr}/^{90}\text{Y}$ beta ray) damage. Application of levosinum shortened the healing time of moist desquamation at each of four dose levels by 5–10 days. In three out of four dose levels used, this shortening of the healing time was significant ($P < 0.03$). Treatment with these topical applications also reduced the incidence of late dermal necrosis and increased ED₅₀ values for the incidence of dermal necrosis, equivalent to a DMF of 1.11–1.13 (Rezvani et al., 2000).

Growth factors

(564) Esculentoside A was reported to protect soft tissues against radiation toxicity through inhibiting the production of several pro-inflammatory cytokines and inflammatory mediators in epithelial cells, macrophages, fibroblasts, and skin tissue (Xiao et al., 2006). Curcumin was found to have a protective effect on radiation-induced cutaneous damage in mice, which was characterised by downregulation of both inflammatory and fibrogenic cytokines in irradiated skin and muscle, particularly in the early phase after irradiation (Okunieff et al., 2006). TGF- β and FGF were found to act individually and synergistically when delivered locally by means of a sustained release system to improve ultimate tensile strength in an acute postirradiation (25 Gy) impaired cutaneous wound-healing model in rats (Tattini et al., 2008).

ACE inhibitors

(565) Captopril inhibited histamine- and serotonin-induced vascular permeability in rat skin (Fantone et al., 1982). Captopril had no effect on epilation in irradiated rat skin, but reduced the incidence of dermal necrosis (Ward et al., 1990a).

Essential fatty acids

(566) Essential fatty acids were administered orally to pigs after skin irradiation ($^{90}\text{Sr}/^{90}\text{Y}$ plaques) in the form of two ‘active’ oils, So-1100 and So-5407, which contained gamma-linolenic acid and a mixture of oil with eicosapentaenoic acid. DMFs were between 1.06 and 1.24 for the acute reactions of bright red erythema and/or moist desquamation, and between 1.14 and 1.35 for the late reactions of dusky/mauve erythema and dermal necrosis. There was the strong suggestion of an effect produced by the ‘placebo’ oil, So-1129, after higher daily doses of oil (Hopewell et al., 1994a,b). Earlier studies with So-1100 had produced DMFs of 1.13–1.24 for acute reactions, and 1.14–1.51 for late erythema or dermal necrosis (Hopewell et al., 1993). Daily dietary supplementation with evening primrose oil reduced the

sensitivity of mouse skin to radiation-induced moist desquamation, and prevented the radiation-associated increase in blood flow (Rahbeeni et al., 2000).

Thiols and prostaglandins

(567) Amifostine has been reported to protect against skin reactions from radiotherapy (Santini, 2001). Mercaptoethylamine, DMSO, and amifostine were tested for their protective effects against doses of 250-kVp x rays producing acute and late skin reactions in rats. All drugs protected skin in both single and fractionated treatment regimens, with mercaptoethylamine giving the most protection and DMSO giving the least protection (Moulder et al., 1977). Low doses of amifostine (0.2–0.3 mg/g) were also used before each of one, five, or 10 fractions given to mouse skin. The degree of protection was similar in all three systems and did not change significantly with fractionation (Rojas et al., 1986). Systemic or topical 16, 16 dm prostaglandin E₂ (16, 16 dm PGE₂) protected against single-dose radiation-induced hair loss (Hanson et al., 1992), and PGE₂ or amifostine protected against fractionated radiation doses (Geng et al., 1992). Three weeks after systemic administration of 16, 16 dm PGE₂ or amifostine, given 1 h before each dose of 2–4.5 Gy per fraction for 10–15 fractions, regrowing hair counts were also increased up to 100% compared with irradiated-only skin sites. The thiol compound effects were slightly superior to the prostaglandin effects in these studies. Local applications of 16, 16 dm PGE₂ or WR-1065 given 15 min before each radiation fraction also enhanced postradiation hair regrowth, although systemic administration of either agent was more effective than the topical route (Malkinson et al., 1993).

Nitroxides

(568) A clinical study demonstrated that topical application of Tempol to the scalp before whole-brain radiation was safe and well tolerated, and evidence of protection against radiation-induced alopecia was observed (Metz et al., 2004). After irradiation of guinea pigs, dry desquamation and gradual hair loss were observed for both control and nitroxide-treated skin; however, over weeks 4–11, postirradiation hair loss was much reduced in nitroxide-treated animals compared with controls (Cuscela et al., 1996).

Adriamycin

(569) Adriamycin has been shown to enhance skin reactions in patients who are receiving or who have received radiation therapy (Donaldson et al., 1974; Cassady et al., 1975). Preclinical studies of acute reactions in mouse skin have shown differing degrees of sensitisation and even protection. It was shown that adriamycin was effective as a potentiating agent when administered during a period when cell depletion in epidermis due to the fractionated radiation was maximal, and before compensatory proliferation had begun. Once compensatory proliferation commenced, the drug lost its enhancing effectiveness (Redpath et al., 1981).

Stem cell replacement

(570) Human mesenchymal stem cells reduced the severity of the response and improved the healing of irradiated leg skin of nude mice (Francois et al., 2007). It was suggested that this strategy might lead to a new therapy for the cutaneous radiation syndrome.

Hyperbaric oxygen

(571) Skin is part of the thermoregulatory system of the body. Hence it is very vasoactive and subject to periods of increased or decreased blood flow depending on prevailing temperature conditions. At lower skin temperatures, blood flow is reduced and there is slight to moderate tissue hypoxia. This hypoxia is sufficient to result in slight radiation resistance. In this situation, hyperbaric oxygen can sensitise skin to radiation. Human skin was reported to be sensitised by up to 40% in terms of dose reduction for equivalent reactions using hyperbaric oxygen (Van den Brenk et al., 1965). In rodents, DMFs of 1.6–2.2 have been reported for leg skin reactions, and 1.2 for skin colonies. Dose modification indicates a homogeneous low level of oxygenation among the target cells in the slightly hypoxic condition (Hendry, 1979). Enhancement of early radiation-induced skin reactions was not observed in clinical trials using the chemical radiosensitiser misonidazole, but in rodents, DMFs of up to 1.3 have been reported. The hypoxia could also be reduced by warming the skin or using pentobarbitol anaesthetics.

(572) Case reports have noted that hyperbaric oxygen treatment given after irradiation has shown some benefit in improving wound healing in irradiated skin (Olascoaga et al., 2008). However, another review concluded that hyperbaric oxygen did not appear to be an effective treatment for radiation-induced fibrosis (Delainian, 2007).

Genetic variability in response

(573) Reactions in skin after irradiation are, like those in other tissues, dependent on the genetic profile of the individual. The classical example is ATM, which is an autosomal-recessive disease affecting one homozygote in 40,000 individuals and heterozygotes at a frequency of 0.5–5%. High radiosensitivity of early skin reactions was reported in children with ATM receiving radiotherapy for cancer (Gotoff et al., 1967; Morgan et al., 1968; Cunliffe et al., 1975). Also, a variety of reports have been published that suggest a correlation between exaggerated reactions after radiotherapy and connective tissue diseases, especially scleroderma, systemic and discoid lupus erythematosus, and mixed connective tissue disease (Koenig et al., 2001). Specifically regarding late reactions, patients with collagen vascular disease, particularly those with scleroderma, have shown increased risk of fibrosis after radiation therapy (Abu-Shakra and Lee, 1993; Morris and Powell, 1997; Chen et al., 2001a,b; Phan et al., 2003).

(574) The incidence of late radiation-induced skin telangiectasia is also known to vary between apparently normal individuals (Turesson, 1989). By comparing skin reactions in left- and right-sided radiotherapy fields in breast cancer patients, it was shown that patient-related factors explained 81–90% of the patient-to-patient

variations in level of telangiectasia, with the other 10–19% being due to random variation (Safwat et al., 2002). Defects in many genes involved in DNA repair, cell-cycle checkpoints, or tumour suppression are known to be associated with the severity of skin reactions (Giotopoulos et al., 2007; Suga et al., 2007). Other studies have used strains of rodents with differing genetic backgrounds to show their relationship to differential radiosensitivity regarding skin reactions (Noda et al., 2005).

Residual injury and recall reactions

(575) Lack of full recovery in tissues after initial irradiation may cause a more severe response to a second treatment. In humans, there is little quantitative evidence pertaining to skin, but some radical radiotherapy treatments to the larynx, performed up to 30 years after moderately high doses given for thyrotoxicosis, were tolerated remarkably well (Hunter and Stewart, 1977). Mouse skin shows good recovery, and there are examples of tolerated retreatment doses of 50–100% of a first tolerance dose for both early and late reactions (Brown and Probert, 1975; Denekamp, 1975; Wondergem and Haveman, 1987; Simmonds et al., 1989; Terry et al., 1989). For radiation-induced necrosis of the mouse tail skin, the tolerance dose was reduced by approximately 10% at times greater than 6 weeks after an initial large dose, and it was reduced further by repeated priming doses (Hendry, 1978). Adriamycin was shown to enhance skin reactions in patients who had previously received radiation therapy (Donaldson et al., 1974). This is a classical case of a radiation ‘recall’ reaction due to residual injury caused by a lack of full recovery. A wide variety of chemotherapeutic agents have now been associated with dermatitis as a radiation recall reaction (Caloglu et al., 2007).

3.3.5. Cardiovascular system

ACE inhibitors

(576) The renin–angiotensin system plays a key role in regulation of haemodynamics in the kidney, lung, and circulatory system. There is, however, no preclinical (Yarom et al., 1993) or clinical evidence of a direct beneficial effect of ACE inhibitors on radiation-induced cardiotoxicity. In humans, there is no specific treatment for cancer-therapy-related cardiomyopathy, and symptomatic patients should receive standard treatments for congestive heart failure including afterload reduction (e.g. ACE inhibitors such as enalapril and captopril) (Yeh et al., 2004; Wouters et al., 2005). There are some indications of a possible beneficial effect of ACE inhibitors after cardiotoxic chemotherapy. In a randomised trial including women treated with high-dose chemotherapy, 114 patients with an elevated risk of developing congestive heart failure were randomised to receive or not receive an ACE inhibitor. In this selected patient group, early treatment with enalapril seemed to prevent the development of late cardiotoxicity (Cardinale et al., 2006).

Amifostine

(577) In a study using rats, a single dose of amifostine administered prior to irradiation was shown to be effective in reducing cardiac damage (Kruse et al., 2003).

Preclinical investigations concerning the selectivity of amifostine on normal tissues and not on tumour are, however, controversial and clinical studies are sparse.

Pentoxifylline

(578) Pentoxifylline inhibits fibroblast proliferation and has also been shown to inhibit intracellular signalling in response to TGF- β and CTGF (connective tissue growth factor). Two experimental studies have shown that pentoxifylline and vitamin E may also have beneficial effects on radiation-induced myocardial fibrosis (inhibition of collagen deposition) and left ventricular function, both when started before irradiation and when started later during the development of radiation-induced heart disease in rats (Boerma et al., 2008a; Liu et al., 2009). The subsequent withdrawal of drugs was, however, associated with a rebound effect, with development of fibrosis.

Stem cell replacement

(579) Coronary heart disease may lead to local ischaemia and the death of cardiomyocytes. For recovery of the damage, both restoration of the local blood flow and regeneration of the lost cardiomyocytes must be achieved. Several studies in recent years have shown that various types of cells, including HSCs, bone-marrow-derived mesenchymal stem cells, and endothelial progenitors, can differentiate into cardiomyocytes *in vitro* and *in vivo* (Jackson et al., 2001; Orlic et al., 2001; Strauer et al., 2002).

(580) In a rat model, it was shown that treatment of myocardial ischaemia with bone-marrow-derived mesenchymal stem cells overexpressing hepatocyte growth factor could be a novel strategy to restore local blood flow and regenerate lost cardiomyocytes (Duan et al., 2003). The therapeutic potential of bone-marrow-derived human mesenchymal stem cells to repair tissue injuries related to side-effects of radiotherapy has also been examined in a mouse model. After transplantation into unconditioned adult mice, human mesenchymal stem cells migrated in bone marrow but also into other tissues. TBI increased human mesenchymal stem cell implantation in bone marrow and muscle, and led to engraftment in brain, heart, and liver (Moussedine et al., 2007). To date, there is no experience in humans with the use of human mesenchymal stem cells to repair radiation-induced cardiac damage.

Anthracyclines

(581) The use of anthracycline-containing therapy has increased over the last decades. Cardiotoxicity of anthracyclines is strongly related to the cumulative drug dose. Doxorubicin doses of $<500 \text{ mg/m}^2$ are usually well tolerated (Steinherz, 1997; Kremer et al., 2001). Anthracyclines release free radicals that damage the cardiac myocytes, which are especially susceptible to free radical damage because of their highly oxidative metabolism and poor antioxidant defences. The free-radical scavenging cardioprotectant, dexrazoxane has been shown to reduce anthracycline-associated myocardial injury in rats (Herman et al., 2001) and in selected studies in humans (Swain et al., 1997). Little is known about a possible interaction

between anthracyclines and radiation on cardiovascular damage. There are some indications from rat studies that the interaction between doxorubicin and local heart irradiation is additive when the treatments are given concomitantly (Wondergem et al., 1998). Several clinical studies showed that anthracycline-containing therapy may further increase the radiation-related risk of congestive heart failure and valvular disorders two- to three-fold compared with radiotherapy alone (Moser et al., 2006; Aleman et al., 2007); this effect may be more than additive (Myrehaug et al., 2008).

Taxanes

(582) Taxanes are frequently used in the treatment of breast cancer. They may lead to acute cardiotoxicity, especially bradycardia. Taxanes interfere with the metabolism and excretion of anthracyclines, and potentiate anthracycline-induced cardiotoxicity, especially at high, cumulative anthracycline doses (Bird and Swain, 2008). There is no reliable information on possible interactions between taxanes and radiation with respect to cardiotoxicity.

Glutamine

(583) Oral glutamine supplementation may enhance the therapeutic index by protecting normal tissues from, and sensitising tumour cells to, chemotherapy and radiation-related injury. There is some information that glutamine supplementation may reduce the incidence of cardiac complications of cancer therapy. However, further studies are needed to define its role in radiation-induced toxicity (Savarese et al., 2003).

Biologicals

(584) Trastuzumab is a monoclonal antibody that targets the human epidermal growth factor receptor tyrosine kinase HER2/ErbB2. This agent has shown a highly significant antitumour effect for patients with HER2-positive breast cancer, and is increasingly used in both the metastatic and adjuvant setting (Piccart-Gebhart et al., 2005; Romond et al., 2005). The ErbB2 receptor is not only expressed on tumour tissue, but also on cardiomyocytes, where it exerts a protective effect on cardiac function. Interference with ErbB2-signalling may block this protective effect. In contrast to anthracycline-induced cardiac toxicity, however, trastuzumab-related cardiac dysfunction does not appear to increase with cumulative dose, does not seem to be associated with ultrastructural changes in the myocardium, and seems to be generally reversible. Trastuzumab is associated with an increased risk of cardiotoxicity (i.e. congestive heart failure and decrease in left ventricular ejection fraction). Information on a possible interaction between trastuzumab and radiation with respect to cardiotoxicity is still scarce. Belkacemi et al. (2008) performed a study in 146 breast cancer patients treated with adjuvant trastuzumab and radiotherapy concomitantly. They observed greater decreases in left ventricular ejection fraction using weekly trastuzumab compared with administration every 3 weeks. Longer follow-up and larger numbers of patients are needed to draw firm conclusions concerning cardiotoxicity following trastuzumab and radiation exposure of the heart.

3.3.6. Eye

(585) Since the first reports of ocular effects of ionising radiation exposure in cyclotron workers (Abelson and Kruger, 1949) and atomic bomb survivors (Cogan et al., 1949), there has been a considerable effort to test and develop pharmacological compounds to prevent or delay radiation-associated eye pathologies (e.g. Langell et al., 2008). To date, such efforts have met with only partial success, as most compounds are either of limited effectiveness or require doses that have significant side-effects. As the lens of the eye is one of the most radiosensitive tissues in the body (Brown, 1997; Ainsbury et al., 2009), and lens opacification can be observed at much lower doses than damage to other eye tissues, the focus of most studies has been in protecting against radiation cataract formation. A brief summary of the literature is given below.

Sulfhydryl compounds

(586) Within 2 years of the first reports of radiation cataract in cyclotron workers and victims of the atomic bombings, it was reported that local or systemic administration of cysteine prevented lid epilation and greatly delayed cataract formation in rabbits whose eyes were exposed to 15 Gy of x rays (Von Sallmann et al., 1951; Von Sallmann, 1952). The authors reported that this finding suggests that the primary site of the protective effect of cysteine occurs in lens fibre cells, which do not contain nuclei. Pirie (1959) expanded on this observation and provided an alternative and mechanistic explanation for the findings by noting, using a much lower x-ray dose of 3 Gy, that cysteine administration itself led to mitotic arrest in the lens epithelium, and that this accounted for its ability to protect against radiation cataract development.

(587) In contrast to the positive findings in the lens, no protective effects were noted in the conjunctiva, cornea, or iris following irradiation. Preliminary investigations of the usefulness of glutathione, thiourea, vitamin E, thioglycolate, and dimer-caprol were also reported, but little to no protection was noted with these agents. In these studies, a relatively high dose of cysteine was administered (up to 800 mg/kg body weight) and lens changes were monitored by ophthalmoscopy, which detects gross changes in lens structure and clarity, rather than slit-lamp examination which was used more often in later reports.

(588) Francois and Behey (1955) reported partial protection of the lens by intravenous pretreatment of rats with 2-mercaptoethylamine. In contrast to Von Sallman, they noted protection against radiation-associated dermatitis and conjunctivitis, in addition to partial reduction of radiation cataract severity, following exposure to 15–25 Gy. Similarly, Swanson et al. (1957) reported that swelling of the lens sutures, an early hallmark of radiation exposure 24–48 h following exposure, was reduced by ocular injection of glutathione 15 min prior to irradiation of the rabbit head with 8–60 Gy. Ocular pathology was only monitored for 48 h following irradiation. Within that time frame, x-ray-associated corneal or iris hyperaemia, corneal oedema, and anterior chamber flare were also reduced by pretreatment with glutathione. Straub and Krause (1958) noted protection of a variety of ocular structures by cysteine

pretreatment prior to exposure of rabbit eyes to 10–20 Gy. Conjunctivitis, epilation, and subsequent cataract formation were reduced by intravenous injection of cysteine up to 2 h prior to irradiation.

(589) A limited study of the effects of cysteine on the cornea, but not any other eye structures, revealed that intraperitoneal injection prevented some x-ray damage but retrobulbar local injection did not (Blodi, 1960).

(590) In subsequent years, more powerful radioprotective sulfhydryl compounds were tested, such as 2-aminoethylisothiuronium bromide (AET) (Hanna and O'Brien, 1963). While protection against early radiation-associated changes, including a drop in mitotic index and abnormal lens fibre histology, was noted after exposure of rats to 24 Gy ^{60}Co , such protection was only seen at near-toxic doses, which limits its clinical usefulness. The authors reported that up to 8 months following irradiation, lid epilation was absent and the severity of cataract was reduced, although the data were not presented. Ismail et al. (1971) tested AET for radioprotection against x-ray-induced cataract-associated changes in guinea pigs following exposure to 4 or 10 Gy. Intraperitoneal injection of 150 mg/kg led to a significant reduction in ^{32}P uptake (as a proxy for mitotic activity) for up to 96 h following exposure compared with irradiated but untreated guinea pigs.

(591) More recently, it was reported that both 2-mercaptopropionylglycine and glutathione isopropyl ester were somewhat effective in delaying lens opacification when administered after 10-Gy x-irradiation (Kobayashi et al., 1992, 1993).

Walter Reed radical scavenging compounds

(592) Intraperitoneal injection of WR-77913 provides some protection against gamma-radiation-induced cataract formation at less toxic concentrations than earlier sulfhydryl compounds in rats exposed to 15.3 Gy of ^{137}Cs (Menard et al., 1986; Osgood et al., 1986). While untreated animals developed dense cataracts within 120 days, WR-77913-treated rats (1160 mg/kg) failed to reach full opacification 200 days after whole-head irradiation. A protective effect was confirmed by analysis of lens hydration and protein insolubilisation, which was similar to that of controls in lenses from treated animals. Radioactive tracer studies indicated that maximum intra-ocular drug concentrations were achieved 15–60 min after intraperitoneal injection (Osgood et al., 1986). Curiously, the highest intra-ocular levels were found in choroid and retina, and the lowest levels were found in lens. The authors speculated that actual WR-77913 concentrations in the single-cell-layered anterior lens epithelium, the presumptive cataractogenic target for ionising-radiation-induced DNA damage, were much higher than in the avascular lens fibre cell mass. Nevertheless, the fairly high concentration, administered within 30 min of irradiation, raises questions about the clinical relevance of such phosphorothioate compounds in humans.

(593) A later report from the same group (Livesey et al., 1995) indicated that doses as low as 350 mg/kg afforded more limited lens protection to rats exposed to 15.3 Gy of ^{137}Cs , and delayed full opacification by 20 weeks. A strong dose–response

relationship was noted at 15 Gy. Exposure to smaller radiation doses appeared to reduce the degree of protection afforded by WR-77913, with only limited protection noted at either 10 or 12.5 Gy. Optimal time of administration was reported as between 30 and 120 min before irradiation; treatment >24 h before or ≥ 30 min after exposure to 15.3 Gy of ^{137}Cs was ineffective in preventing cataract formation.

(594) Similar findings were reported using amifostine 500 mg/kg (WR-2721) administered 30 min prior to ^{137}Cs irradiation of rats (Reddy et al., 1989). Light microscopic analysis of lens morphology suggested that this concentration of amifostine was more effective than WR-77913 1160 mg/kg in preventing lens fibre cell swelling and disruption of the bow region. However, WR-2721 250 mg/kg was completely ineffective in preventing radiation-induced lens changes. The authors speculated that the increased efficacy of WR-2721 over WR-77913 might be related to its greater ability to lower the phase-separation temperature of soluble lens proteins in vitro.

(595) The rapid clearance of WR compounds and their relatively low toxicity compared with other sulfhydryl agents suggests that a topically applied ocular formulation might be useful in delaying or preventing lens opacification, although no such studies have been reported. Such a course of treatment might be useful for preventing cataract formation following TBI, for example, where even with eye shielding, the incidence of radiation cataract is greater than 30% (Van Kempen-Harteveld et al., 2003).

(596) The precise mechanisms by which WR-77913 or WR-2721 delays cataract formation is unknown. The finding that the drug is of limited effectiveness when given after irradiation suggests that it may inhibit initiating or early steps in radiation cataract formation. This observation is consistent with the role of phosphorothioate compounds as free radical scavengers or in their ability to maintain high levels of reduced glutathione. On the other hand, the inability of this compound to prevent lens opacification at lower radiation doses suggests that its role as an inhibitor of protein phase separation, maintaining lens soluble protein and reducing light scattering, may be the operative mechanism. While radiation cataract following exposure to low-dose ionising radiation is believed to result from damage to dividing lens epithelial cells and subsequent aberrant differentiation and migration (Worgul et al., 1989; Worgul et al., 1991; Meecham et al., 1994), high-dose exposures may directly affect lens fibre cell proteins and membranes, and the distribution of lens proteins into soluble or light-scattering insoluble fractions. This hypothesis is supported by the finding that WR-77913 prevents or delays lens opacification caused by other insulting agents such as selenite or UV exposure (Roberts et al., 1991; Clark and Steele, 1992).

Metalloporphyrins

(597) Some metalloporphyrins have free radical scavenging ability. The SOD mimetic manganese (III) tetrakis(1-methyl-4-pyridyl) porphyrin (MnTMPyP) was evaluated for its protective efficacy in rats irradiated with 8- or 28-Gy protons 1 h after direct intra-ocular injection of the compound (Mao et al., 2009). The acute ocular inflammatory response induced by 28 Gy was significantly reduced in MnTMPyP-

treated animals. By 6 weeks, 75% of irradiated but untreated animals had severe lens opacification compared with 0% in the MnTMPyP-treated group. Approximately 25% of these treated animals exhibited more minor, Grade 1 opacity. Retinal photoreceptor damage was significantly reduced at 6 and 9 months following 28-Gy proton irradiation of MnTMPyP-treated rats compared with untreated, irradiated animals. Similarly, the retinal microvasculature was almost completely preserved in treated animals irradiated with 28 Gy compared with extensive vascular damage in untreated, irradiated retinas. A dose of 8-Gy proton irradiation did not result in retinal vascular changes in either treated or untreated eyes. Caspase-3 measurements in 28-Gy-irradiated treated and untreated retinal sections indicated massive levels of apoptotic cells, whereas only a small number of apoptotic cells were seen in MnTMPyP-treated animals.

Antioxidants

(598) The nitroxide free radical spin trap and SOD mimic Tempol has been reported to reduce the severity of radiation-induced cataract formation in rabbits following exposure to 11-Gy x-irradiation (Sasaki et al., 1998). Tempol was injected into the anterior chamber 15 min prior to irradiation, and cataract progression was followed for up to 19 weeks by slit-lamp examination. A similar reduction in the frequency of x-ray-induced DNA single-strand breaks, measured by the Comet assay, was noted in lens epithelial cells from irradiated animals. While intriguing, the rapid bioreduction of Tempol to its oxidised form limits the usefulness of this approach therapeutically.

(599) Carnitine, and its metabolites, is reported to have antioxidant and ROS scavenging properties (Vanella et al., 2000), and it has been suggested that its protective effect against lipid peroxidation might be useful as an anticataract agent. To test this, rats were exposed to a single 5-Gy dose of ^{60}Co with or without L-carnitine (100 mg/kg intraperitoneally from 1 day before to 10 days after irradiation) (Kocer et al., 2007). A significant decrease in lens opacity was noted in the carnitine-treated animals at 10 days. In addition, the elevation in lens malondialdehyde level noted in untreated, irradiated animals was completely prevented by carnitine treatment. Curiously, lens levels of both SOD and GSH-Px were elevated in carnitine-treated animals. The authors interpreted this finding as evidence for an early protective response to radiation-induced oxidative damage facilitated by carnitine administration. However, the irradiated animals were only followed for 10 days after exposure, and longer-term follow-up would provide stronger evidence for a radioprotective effect. Carnitine also has anti-osmolytic properties, and has been suggested to protect the lens from osmotic stress in an animal model of diabetic cataract formation (Pessotto et al., 1997).

(600) Recent work suggests that carnitine 200 mg/kg/day or vitamin E 40 mg/kg/day are also protective against radiation-induced retinal damage, as measured by changes in thickness of the retinal cell layer (Sezen et al., 2008) 10 days after irradiation with 15 Gy of ^{60}Co . It should be noted that, in comparison with radiation-induced lens pathology, much higher doses of radiation are required to damage retinal tissue.

(601) Other studies (Karslioglu et al., 2004) showed that pretreatment of rats with vitamin E 10 mg/kg/day reduced the radiation cataract grade, inhibited radiation-induced elevation in lens malondialdehyde, and inhibited elevation of GSH-Px and SOD. However, the failure to follow animals for >10 days following exposure is a significant concern regarding the long-term efficacy of vitamin E in preventing radiation cataracts.

(602) Long-term administration of *Ginkgo biloba* extract (which has antioxidant and anti-inflammatory properties), resulted in a significant increase in the time of onset of lens opacification following irradiation of rats with 12 Gy, but treatment had no effect on the subsequent rate of opacification when rats were followed for up to 21 weeks (Worgul and Droy-Lefaix, 1999). The authors suggested that the relatively high dose of x rays resulted in 'saturation' which obscured any potential effect of *Ginkgo biloba* on rate of progression, but no follow-up studies were reported.

(603) In a similar but much shorter study, rats received *Ginkgo biloba* orally for 3 days prior to and 7 days after cranial irradiation with 5 Gy. At 10 days after irradiation, there was a significant reduction in severity of lens opacity in the *Ginkgo-biloba*-treated group, as well as a reduction in lens malondialdehyde levels and increased SOD and GSH-Px levels. In contrast to the radioprotective effects, *Ginkgo biloba* did not reduce cataract severity in a rat selenite model, in which lens oxidative stress is believed to be an early or initiating factor (Orhan et al., 1999).

Hormonal manipulation

(604) The cell cycle of the lens epithelium of northern leopard frogs was manipulated by hypophysectomy (to halt mitotic activity) and pituitary hormone administration (to stimulate baseline mitosis and reverse hypophysectomy-induced mitotic suppression). Also, hypophysectomised-irradiated animals received varying concentrations of replacement hormone in order to quantitatively modulate lens epithelial mitotic activity and determine the effect on cataractogenesis. It was found that irradiated, hypophysectomised (mitosis halted) frogs failed to develop opacities, while those with hormonal replacement (mitosis re-instated) developed cataracts (Holsclaw et al., 1994).

(605) A series of recent papers reported both negative and positive radioprotective effects of oestrogen in ⁶⁰Co gamma-irradiated rat eyes. Oestradiol given to ovariectomised female rats prior to irradiation increased both the rate and incidence of lens opacities (Dymlacht et al., 2006). In contrast, the same compound administered following irradiation, via subcutaneous slow release, had significant protective effects (Dymlacht et al., 2008). Further studies demonstrated that the oestrogen effect was limited to females, as male rats implanted with 17-β-oestradiol showed no difference in the incidence of radiation cataracts after exposure to 10 Gy of ⁶⁰Co (Henderson et al., 2009). Male rats had a significantly greater incidence of PSC cataracts than females when animals were followed for up to 500 days after irradiation, although no gender-based differences in rate of progression of such changes were observed. The authors speculated that other hormones, in addition to oestrogen, may contribute to gender-based differences in the incidence of radiation cataracts.

(606) In contrast to the findings with low-LET exposure, male rats implanted with $17\text{-}\beta\text{-oestradiol}$ and exposed to 1-Gy high-LET ^{56}Fe ions exhibited greater incidence and rate of progression of lens opacities compared with untreated males (Henderson et al., 2010). The authors speculated on a molecular basis for these differences by suggesting that the predominantly ROS-mediated spectrum of DNA damage caused by low-LET radiation may be hormonally regulated in a different fashion than the direct DNA damage and DNA damage ‘clusters’ typically induced by high-LET exposure.

Hypoxia

(607) Hypoxia does not appear to prevent the onset or progression of radiation cataracts (Bennett et al., 1953; Darden et al., 1968). In contrast, ligation of the right common carotid artery, resulting in reduced ocular blood flow, in rats 15 or 38 days after irradiation with 4.4-Gy x rays, led to accelerated cataractogenesis in the lens on the affected side (Koch et al., 1974). The authors hypothesised that reduced blood flow and availability of metabolic substrates or nutrient delivery to irradiated lens epithelial cells in the affected lens would result in faster progression of lens opacification.

DMSO

(608) Topical ocular pretreatment with 10% DMSO in mice was effective in preventing total lens opacification after whole-head irradiation with 10-Gy x rays (Hagemann et al., 1970). While no dense opaque cataracts were observed in treated animals, a time-dependent progression of lens opacification was noted. Increasing the x-ray dose to 14 Gy did not reduce the effectiveness of DMSO in preventing total lens opacification. DMSO treatment following irradiation was completely ineffective.

(609) With regard to a possible mechanism for the protective effect of DMSO, the authors noted that DMSO treatment transiently reduced DNA synthesis in the lens epithelium by 50%, consistent with the theory that the primary target for radiation cataract is the germinative zone of the lens epithelium.

(610) In contrast to reported lens protection, topical administration of 10% DMSO resulted in corneal radiosensitisation in mice (Hagemann et al., 1970). Corneal lesions were observed in 50–80% of treated mice but not in irradiated controls. The apparent corneal radiosensitisation suggests that DMSO and related compounds may have limited usefulness in limiting eye radiation effects.

Bowman–Birk inhibitor concentrate

(611) Mice fed Bowman–Birk inhibitor concentrate (BBIC), a protease inhibitor, in their diet before and after exposure to 0.50 Gy of ^{56}Fe HZE (high-Z, high-energy) particles had reduced prevalence and severity of radiation-associated opacification up to 24 months following irradiation (Davis et al., 2010). In contrast, mice fed BBIC before and after irradiation with 0.30-Gy protons did not exhibit reduction in cataract formation. The authors suggested that the relatively high dose of protons resulted in extensive lens damage that was not reduced by BBIC treatment. In the same paper, the authors also reported radioprotection using an antioxidant formulation containing a variety of compounds, including alpha-lipoic acid, ascorbic acid,

co-enzyme Q10, N-acetyl cysteine, selenomethionine, and vitamin E. Similar to the findings with BBIC, the antioxidant formulation resulted in significant protection against HZE-particle-induced cataractogenesis but no significant protection against proton irradiation.

Sugars

(612) A high galactose diet (30%) reduced radiation-induced lens damage in mice, evaluated by light and electron microscopy (vacuole formation, fibre cell swelling, and morphological disorganisation) (Kodama et al., 1983). These observations were confirmed by slit-lamp examination of irradiated mice lenses for up to 4 months (Taura et al., 1985). The protective effect was noted whether treatment was initiated 1 week before or as much as 1 week after irradiation with 11 Gy. This is surprising as sugars are believed to exert their radioprotective effect by scavenging short-lived free radicals formed during irradiation.

3.3.7. Respiratory system

Antioxidants

(613) Radiation-induced lung damage is associated with prolonged oxidative stress, at least during the acute pneumonitis phase of damage. Experimental studies showed that overexpression of extracellular superoxide dismutase (EC-SOD) in transgenic mice decreased oxidative stress and conferred protection against radiation-induced lethal pneumonitis, as well as reducing the macrophage infiltration and TGF- β expression, after whole-lung irradiation (Kang et al., 2003). Subsequent studies confirmed that the protective effect of EC-SOD overexpression was, at least in part, due to attenuation of the macrophage response, as well as decreased TGF- β activation and downregulation of the profibrotic TGF- β -Smad3 signalling pathway (Rabbani et al., 2005). These studies suggest that EC-SOD could be a useful therapeutic agent for protection against the oxidative products and inflammatory response generated after lung irradiation.

(614) Another experimental rat model demonstrated that both MnSOD and CuZnSOD were effective at reducing micronucleus formation in fibroblasts when given 30 min before or immediately after whole-lung or lower-lung irradiation (Khan et al., 2003). A SOD-catalase mimetic, which inhibits both intracellular and extracellular ROS, also inhibited micronucleus formation when given either before or up to 2 weeks after lung irradiation (Langan et al., 2006). The greatest protection was seen when the drug was given after irradiation, indicating that the effects were mediated largely via inhibition of secondary inflammatory responses rather than direct protection against radiation-induced DNA damage. However, the SOD-catalase mimetic given during the first 3 days after irradiation did not reduce functional lung damage and morbidity at 3–4 months after irradiation (Langan et al., 2006). The authors concluded that the SOD-catalase mimetic given shortly after lung irradiation was effective in inhibiting the initial wave of ROS induced by the inflammatory response initiated by irradiation, but that more prolonged treatment was required to suppress the effects of the chronic inflammatory response.

Thiols and radical scavengers

(615) Amifostine is the most effective and widely tested of the radical-scavenging radiation protectors available for clinical use. Preclinical studies have been consistent in demonstrating significant protection against radiation-induced lung damage in rodents treated with either single dose or fractionated thoracic irradiation. Significant reductions in lethal pneumonitis at 9 months after irradiation were preceded by improved endothelial cell function and type II pneumocyte function, assessed from biochemical assays of bronchial lavage fluid at 1 month after irradiation, in amifostine-treated animals (Travis et al., 1987). Separate studies also demonstrated that amifostine reduced the radiation-induced rise in TGF- β levels in plasma 1–3 months after thoracic irradiation, and reduced the accumulation of macrophages and expression and activation of TGF- β in irradiated lung tissue at 6 months after irradiation (Vujaskovic et al., 2002b). In those studies where dose–response relationships were investigated, protection factors for lethal pneumonitis at <9 months after irradiation in air were in the range of 1.2–1.4 (Down et al., 1984; Parkins et al., 1984; Travis et al., 1984, 1987). Protection factors for late fibrosis at >1 year after irradiation were generally slightly higher, in the range of 1.5–1.7 (Down et al., 1984; Travis et al., 1984). Higher protection factors were also seen for fractionated irradiations with mice breathing 10% oxygen during irradiation (Parkins et al., 1984). This supports the hypothesis that the degree of radioprotection in tissues is dependent on oxygen tension, being maximal at intermediate oxygenation (Denekamp et al., 1982).

(616) There is also evidence for radioprotection of lung tissue in some clinical trials, although the results are variable. A multicentre phase 3 randomised trial was carried out to investigate the protective effects of amifostine given daily with conventional radiotherapy for advanced lung cancer (Antonadou et al., 2001). The incidence of acute pneumonitis and late lung fibrosis was significantly reduced in the amifostine-treated patients (9% vs 43% Grade 2 pneumonitis; 28% vs 53% fibrosis at 6 months). Amifostine was generally well tolerated but 7% of patients developed transient hypotension. Two subsequent randomised trials demonstrated protective effects with amifostine given daily with concurrent chemoradiotherapy (Antonadou et al., 2003) or twice per week with hyperfractionated radiotherapy with concurrent chemotherapy (Komaki et al., 2004). The incidences of Grade 3 pneumonitis were reduced from 56% to 19% (Antonadou et al., 2003), or from 16% to 0% (Komaki et al., 2004) in patients receiving amifostine during chemoradiotherapy. However, another large randomised trial did not show any protective effect of amifostine in patients treated with hyperfractionated radiotherapy and chemotherapy for lung cancer (Movsas et al., 2005).

Anti-inflammatory and anticoagulant agents

(617) There is abundant preclinical evidence to show that chronic administration of steroidal anti-inflammatory drugs can decrease the acute inflammatory response in irradiated rodent lungs (Michalowski, 1994; Moulder et al., 1998). A marked reduction in mortality after thoracic irradiation has also been shown for steroids

given during the pneumonitis phase of damage (LD_{50} increased by 20–50%) (Phillips et al., 1975; Gross, 1980; Gross et al., 1988). This is probably due, at least in part, to inhibition of radiation-induced capillary permeability and protein leakage into the pleural cavity. Steroids given after the pneumonitis phase also inhibited lung damage, but there was a rapid deterioration once steroids were withdrawn. Some non-steroidal anti-inflammatory inhibitors of cyclo-oxygenase (e.g. aspirin) or the lipoxygenase pathway (e.g. diethylcarbazine) have been shown to protect against lethal radiation pneumonitis, although other cyclo-oxygenase inhibitors, such as ibuprofen, offered little protection and indomethacin accelerated mortality in mice (Gross et al., 1991). Although there is clinical evidence that steroids can relieve the symptoms of pneumonitis, it remains unclear whether they can protect against the development of late fibrosis.

(618) It is also possible to target the inflammatory component of radiation-induced lung injury using statins. Although originally developed as lipid-lowering agents for treatment of hypercholesterolaemia and atherosclerosis, statins are potent anti-inflammatory and antithrombotic agents. They downregulate expression of several inflammatory cytokines and their receptors (Morikawa et al., 2002), and increase endothelial cell production of antithrombotic eNOS and thrombomodulin (Laufs, 2003). An experimental study in mice showed that lovastatin was effective in inhibiting recruitment of macrophages and lymphocytes to irradiated lung. Drug given repeatedly from the time of irradiation or starting 8 weeks after irradiation, prior to the onset of pneumonitis, also reduced the subsequent collagen deposition in the irradiated lung and increased animal survival, although there was no reduction in the breathing rates during the pneumonitis phase of damage (Williams et al., 2004).

(619) Pentoxifylline is an antithrombotic drug that inhibits platelet aggregation by stimulating the release of prostacyclin and inhibition of phospholipase A2 and $TNF\alpha$ production. It also improves perfusion through small capillaries by increasing the deformability of red blood cells. Chronic administration of pentoxifylline has been shown to reduce pulmonary hypoperfusion at 40 weeks after irradiation of rat lung, although no modification of early endothelial cell dysfunction or acute lung injury was seen (Ward et al., 1992; Koh et al., 1995). In a randomised clinical trial of breast or lung cancer patients, pentoxifylline given during the period of radiotherapy significantly reduced both early (3 month) and late (6 month) lung toxicity, assessed from objective LENT-SOMA (Late Effects in Normal Tissue/ Subjective Objective Management Analytic) scores and functional perfusion scans (Ozturk et al., 2004).

ACE inhibitors and AII receptor antagonists

(620) Ward et al. demonstrated the protective effect of ACE inhibitors on radiation pneumotoxicity in a series of experiments in rats. Captopril (a thiol-containing ACE inhibitor) protected against radiation-induced changes in endothelial function (increases in production of prostacyclin and thromboxane, and reductions in ACE activity and plasminogen activator) in irradiated rat lung (Ward et al., 1988, 1992). Dose reduction factors of 1.4–2.1 were calculated for markers of endothelial

function in captopril-treated rats. Captopril also decreased the hydroxyproline content of the irradiated lung (Ward et al., 1990b), blocked the radiation-induced hypertension, and reduced the transient increase in lung density seen at 4–8 weeks after high-dose hemithorax irradiation (Ward et al., 1993). However, rats had to be maintained on captopril for beneficial effects; rapid deterioration of lung density was seen if the drug was withdrawn from the rats at 3 months after irradiation (Moulder et al., 1998). The mechanisms whereby captopril protects against radiation lung damage are thought to include both ACE inhibition and a non-specific thiol effect, the latter being particularly important for inhibition of fibrotic effects (Ward et al., 1989; Moulder et al., 1998). However, an angiotensin II type 1 receptor blocker was found to be just as effective as thiol-containing ACE inhibitors for inhibition of pneumonitis and fibrosis after lung irradiation (Molteni et al., 2000). This suggests that activation of the angiotensin receptors is involved in the development of radiation pneumonitis.

(621) Despite the encouraging preclinical results, a retrospective clinical analysis of lung cancer patients who received ACE inhibitors during radiotherapy (mostly for hypertension) concluded that this did not significantly reduce the risk of radiation pneumonitis (Wang et al., 2000).

Growth factors

(622) Numerous studies have demonstrated TGF- β activation and increased signalling in irradiated tissues. In the irradiated lung, this has been shown to precede the development of fibrosis (Finkelstein et al., 1994; Rube et al., 2000). Several experimental approaches have been tested to inhibit this TGF- β activation and thereby ameliorate damage in the irradiated lung. Recombinant human adenoviral vector carrying the soluble TGF- β type II receptor gene increased the levels of circulating soluble receptors in treated rats at 1–2 days after administration, consequently reducing the lung tissue levels of active TGF- β (Rabbani et al., 2003). A single administration of the vector 1 day before right lung irradiation decreased the number and activity of macrophages in irradiated lung, and decreased the histological and functional lung damage at 4 or 8 weeks after irradiation (Rabbani et al., 2003; Nishioka et al., 2004).

(623) In an alternative approach, neutralising antibodies were shown to be effective in reducing radiation-induced lung damage in rats (Anscher et al., 2006). A single injection of the anti-TGF- β antibody, given immediately after fractionated irradiation to the right lung, reduced macrophage accumulation, TGF- β activity, and alveolar thickness at 6 weeks after irradiation. Six months after irradiation, there was a significant reduction in TGF- β activation and downstream target proteins Smad3 and phosphorylated Smad2/3, as well as reduced collagen deposition, in the lungs of the antibody-treated rats. These results suggest that the neutralising antibody acts at tissue level to decrease the availability of TGF- β . Similar protective effects were seen when a small molecule TGF- β type 1 receptor kinase inhibitor was given continuously in food from 1 week before irradiation (Anscher et al., 2008). Drug-treated rats had less histological lung damage, fewer breathing difficulties, less oxidative stress and TGF- β expression in the lung tissue, and less lung fibrosis than

rats given the control food. Drug treatment for only 3 weeks after irradiation was less effective than continuous drug administration.

(624) Recombinant human keratinocyte growth factor (rHuKGF) mediates epithelial cell proliferation and differentiation. Pretreatment with rHuKGF has been shown to decrease alveolar type II cell loss, pulmonary oedema, and TGF- β expression in experimental models of bleomycin and acute radiation-induced lung injury (Yi et al., 1996, 1998; Chen et al., 2004). rHuKGF given immediately after fractionated lung irradiation also gave a significant reduction in both acute pneumonitis and late lung fibrosis, which was associated with reduced expression of integrin $\alpha\beta 6$ and TGF- β activity (Chen et al., 2004). These data indicate that restoration of the integrity of the pulmonary epithelium during the acute phase of radiation injury can lead to downregulation of integrin-mediated TGF- β activation and late fibrosis.

(625) Some experimental studies have shown that the growth factor bFGF protected against early radiation-induced apoptosis in endothelial cells, and reduced the incidence of lethal pneumonitis after bilateral lung irradiation with a mediastinal block to shield the heart (Fuks et al., 1994). Other studies found only a low incidence of early apoptosis (<1%), and no protection against lethal pneumonitis when the whole thorax was irradiated (Tee and Travis, 1995).

3.3.8. Urinary system

Anti-inflammatory agents

(626) High-dose steroids given together with fractionated renal irradiation increased the severity of glomerular and vascular lesions in rats (Berdjjs, 1960), and decreased survival time in rabbits (Caldwell, 1971). However, later studies using chronic low-dose administration of dexamethasone demonstrated a delay in the progression of radiation nephropathy and prolongation of animal survival in rats, with DMFs of 1.2–1.3 (Geraci et al., 1995). The combination of dexamethasone with captopril was more effective than either drug alone. A similar inhibition of radiation nephropathy (DMF = 1.2) was seen in mice treated with continuous high-dose acetylsalicylic acid given in the drinking water from the time of single-dose irradiation (Verheij et al., 1995). Lower drug doses combined with fractionated irradiation were, however, much less effective (Van Kleef et al., 2000). Chronic administration of the antiplatelet drug clopidogrel did not inhibit fibrin deposition in glomeruli, or alter the time of expression of kidney damage after fractionated irradiation of mice (Te Poele et al., 2001).

(627) The anti-inflammatory agent retinoic acid exacerbated experimental radiation nephropathy in a rat model of TBI/BMT nephropathy when given continuously from the onset of moderate proteinuria and azotemia (Moulder et al., 2002). There are also clinical reports of enhanced radiation nephropathy in patients treated with retinoic acid in combination with TBI/BMT (Turman et al., 1999). This may have been due to inhibition of renal nitric oxide production.

(628) Daily administration of meclofenamate (inhibitor of prostaglandin synthesis) inhibited acute cystitis in monkeys at 3 weeks after high single-dose pelvic irradiation (Ambrus et al., 1984). Local or systemic application of acetylsalicylic acid also improved the function of irradiated mouse bladders during the acute phase of damage (Dorr et al., 1998).

ACE inhibitors and AII receptor antagonists

(629) One of the most successful approaches to prevention or amelioration of radiation-induced injury in the kidneys is by inhibition of the renin–angiotensin system. Initial studies suggested that vasoactive compounds such as captopril could inhibit radiation-induced impairment of renal function in the pig (Robbins and Hopewell, 1986). Extensive studies by Moulder's group subsequently demonstrated that both ACE inhibitors and AII receptor antagonists effectively inhibited development and progression of renal damage in rats after TBI and BMT, or after bilateral renal irradiation (Moulder et al., 1998, 2007; Robbins and Diz, 2006).

(630) Moulder et al. (1993) demonstrated that ACE inhibitors could be used to treat established radiation nephropathy when treatment was started 6 months after bilateral fractionated renal irradiation. Azotemia and proteinuria were reduced and animal survival was increased in groups treated with either captopril or the non-thiol ACE inhibitor enalapril. They subsequently demonstrated that both of these drugs inhibited the development of radiation injury after TBI/BMT, with DMFs of 1.2–1.5, when given prophylactically from the time of irradiation. AII type 1 receptor antagonists were even more effective than ACE inhibitors, whereas non-ACE inhibitor antihypertensive drugs were ineffective (Moulder et al., 1993, 1996, 1998; Cohen et al., 1994). The protective effects of captopril were shown to persist in animals treated for 26 weeks after TBI/BMT but then removed from the drug. Beneficial effects of captopril were also seen after only a short treatment, from 3.5 to 9.5 weeks after TBI/BMT. The protective effects of the inhibitors are therefore exerted during the initial development of proteinuria and before the onset of azotemia or increased blood pressure. Both ACE inhibitors and AII receptor antagonists effectively inhibit radiation nephropathy, although there is no evidence for radiation-induced increases in systemic levels of AII or renin. This suggests that they may be acting by inhibition of AII generated locally within the kidney (Robbins and Diz, 2006).

(631) These very promising preclinical studies led to a prospective, randomised trial to test the efficacy of captopril in reducing BMT nephropathy in humans. Initial results from a series of 55 patients who received TBI/BMT showed a trend for increased survival and improved renal function in favour of the captopril-treated group (Cohen et al., 2008).

Growth factors

(632) A single injection of palifermin (rHuKGF) given 2 days before single-dose pelvic irradiation significantly protected against both acute and late bladder dysfunction (Jaal and Dorr, 2007). The ED₅₀ for reversible acute damage increased from 20

to 27 Gy, and the EC₅₀ for late damage increased from 16 to 22 Gy (DMFs of 1.35 and 1.38, respectively). Palifermin given after irradiation had no protective effect. Palifermin modified both proliferation and differentiation in epithelial and endothelial cells, and transiently increased proliferation of urinary epithelium has been shown in both rats and monkeys (Yi et al., 1995). However, very little urothelial cell depletion occurs during the acute period after irradiation, so the protective effects of palifermin in bladder may be related to its ability to inhibit inflammatory reactions or protect the microvascular endothelial barrier function in irradiated tissue (Gillis et al., 1999; Jaal and Dorr, 2007). The positive effect of palifermin on late bladder damage was presumed to be due to protection against severe early damage with subsequent reduction of consequential late damage (Dorr and Bentzen, 1999; Jaal and Dorr, 2007).

3.3.9. Musculoskeletal system

(633) Comparatively little work has been performed with radiation response modifiers in the musculoskeletal system relative to many other organ systems.

Free radical scavengers

(634) Various free radical scavengers, including ascorbate, riboflavin, and mannitol, have been used to reduce the effect of high-dose radiation on bone, as used for sterilisation of bone grafts for tissue banking. The benefit of such compounds in the context of the radiation doses that are commonly used for therapeutic irradiation of cancers has not been evaluated. However, there are concerns related to tumour protection with the use of such compounds.

(635) Among the various radioprotectors that have been tested in the clinical dose range, amifostine has received the most attention, but the literature is somewhat inconsistent with regard to its efficacy. For example, while amifostine protected against skin toxicity, it did not affect tibial growth in weanling rats (Constine et al., 1987). On the other hand, another group of investigators showed that amifostine was rather effective in reducing radiation-induced bone inhibition in rabbits (Forrest et al., 2002; La Scala et al., 2005). Other studies have shown modest protective effects of amifostine alone, but enhanced effects when combined with pentoxifylline and misoprostol or with selenium (Damron et al., 2004, 2006). Pentoxifylline alone has been shown to protect against radiation-induced growth plate injury (Pateder et al., 2002).

(636) Melatonin appears to have some protective effect on growing bone in rats (Topkan et al., 2008). In this particular study, the protective effect of melatonin was actually greater than that of amifostine, and the addition of amifostine to melatonin did not confer additional protection.

(637) Some other compounds have also been tested in animal models of radiation-induced bone loss or growth inhibition. For example, arsenic trioxide has been shown to reduce bone loss after radiation therapy, as well as exhibiting anti-cancer and anti-angiogenic properties (Kumar et al., 2008). Not unexpectedly,

diphosphonate appears to reduce the adverse effects of radiation on bone formation (Ubios et al., 1986).

Growth factors

(638) The growth factor, bone morphogenic protein 2 is undergoing testing as an inducer of osteoblast differentiation, and has also been tested as a radiation response modifier (Springer et al., 2008). Interestingly, in that study, both bone morphogenic protein 2 and bFGF, when applied alone, enhanced postradiation bone formation. In contrast, when the two growth factors were given together, they had an adverse effect on osteogenesis.

Hyperbaric oxygen

(639) Hyperbaric oxygen therapy has been shown to have a positive effect in a number of delayed radiation injury situations, including musculoskeletal radiation injury (Feldmeier and Hampson, 2002). Hyperbaric oxygen remains somewhat controversial, however, because of the difficulties with endpoint assessment and the problems associated with conducting randomised clinical trials.

Stem cells

(640) There is even less information about the use of traditional radiation response modifiers for radioprotection of skeletal muscle. However, one area that has received considerable attention relates to the satellite cells of skeletal muscle. These cells, located beneath the basal lamina that surrounds each myofibre, are precursors for muscle growth and repair. Satellite cells play an essential role in maintaining the health of skeletal muscle, and have received considerable attention because they exhibit some properties of stem cells. After various types of experimental injury, including radiation injury, satellite cells are capable of proliferating and regenerating new myofibres (Adams et al., 2002; Collins et al., 2005). While the utility of this concept in radiation injury needs further development, it appears that harnessing the capabilities of satellite cells may hold promise as an approach to prevent or reverse radiation-induced muscle damage.

3.3.10. Endocrine system

Diagnosis and management of radiation-induced growth hormone deficiency

(641) All children who have received cranial irradiation as part of their cancer therapy should undergo regular growth monitoring until final adult height is reached. Accurate measurement of standing and sitting height is recommended every 3–6 months (Scottish Intercollegiate Guidelines Network, 2004). In children who have previously had cranial irradiation, significant growth deviation over a 12-month period (defined as growth rate below the 25th centile or a reduction in height of >1 standard deviation), in the absence of other aetiologies, is highly suggestive of clinically significant GH deficiency.

(642) Children with impaired growth rate should be tested for GH levels. GH deficiency is defined by an attenuated GH response to pharmacological stimuli. While

24-h sampling of spontaneous GH secretion may be the most sensitive method of determining GH status, it is clinically impractical. The insulin tolerance test is the universally accepted 'gold standard' for assessment of GH deficiency in irradiated patients (Lissett et al., 2001). Standard provocation tests may yield false-negative results, particularly following low-dose cranial irradiation, and must be interpreted cautiously. Reduction in GH-dependent markers, IGF-1 and IGF binding protein 3, are consistent but not specific for GH insufficiency, and may provide additional biochemical information (Shalet et al., 1998).

(643) GH replacement in children with radiation-induced GH deficiency increases growth rate, and the GH response is comparable to that seen in children with idiopathic GH deficiency, at least in the short term. Continuation of GH to final height will maintain the initial height centile and prevent further loss in stature rather than produce catch-up growth, as would be the role in classical GH deficiency (Clayton et al., 1988a,b; Sulmont et al., 1990). The cause of this suboptimal GH response is probably multifactorial and likely to include spinal irradiation, precocious puberty, and delayed initiation and inadequacy of GH therapy.

(644) Concern has been raised over the safety of GH replacement therapy in childhood cancer survivors, although these concerns have not been substantiated. The risk of relapse is greatest within the first 2 years after diagnosis. Data from single and large multicentre surveillance studies showed no increase in the risk of tumour recurrence or incidence of de-novo malignancies in children treated with GH replacement, initiated 2 or more years after completion of primary treatment (Shalet et al., 1997; Price et al., 1998; Swerdlow et al., 2000). GH therapy is recommended for children with proven GH deficiency but with a good prognosis at 2 years after treatment. When the cause of growth impairment is unclear, a trial of GH may be appropriate (Scottish Intercollegiate Guidelines Network, 2004).

(645) GH production increases two-fold during puberty, and despite previous recommendations to stimulate GH in pubescent childhood cancer survivors, there is no convincing evidence of any additional benefit. Higher GH doses may be detrimental to these patients by accelerating skeletal maturation and shortening pubertal duration. Promising preliminary results are emerging from an alternative approach combining a GnRH analogue with GH replacement to halt pubertal progression and delay epiphyseal closure, and thus prolong linear growth (Adan et al., 2000; Mericq et al., 2000). In children receiving cranial irradiation alone, gain in statural height is a consequence of better spinal growth. However, for those who have received cranio-spinal irradiation, skeletal disproportion may be exacerbated as height gain will be due to leg growth.

(646) GH deficiency is permanent and lifelong therapy is recommended. Active follow-up of adult survivors is essential for ongoing management of endocrinopathies.

Screening and management of radiation-induced thyroid disorders

(647) Clinical assessment is of limited value in the detection of thyroid nodules, while routine ultrasound may be an overly sensitive screening tool as thyroid nodules are reported in 35–40% of autopsies or surgery in the general population (Gleeson

et al., 2002). Radioisotope scanning is currently under evaluation. It is recommended that survivors of childhood cancer who have received radiotherapy to the neck, brain, or spine should undergo clinical assessment and have thyroid function checked at the end of treatment and at regular intervals thereafter for life (Scottish Intercollegiate Guidelines Network, 2004). There are no good-quality studies that address the question of screening for thyroid nodules or second primary thyroid cancers. At-risk survivors should be advised accordingly and asked to seek urgent medical advice if they notice a palpable neck mass.

(648) Thyroid hormone replacement therapy is safe and effective, although cautious introduction is necessary in patients previously exposed to anthracyclines who are at risk of cardiac dysfunction. There is no evidence to support or refute the use of thyroxine in compensated hypothyroidism, although it is arguable that supplementation is warranted in these patients as hyperstimulation with persistently elevated TSH may theoretically predispose to malignant change.

Management of ACTH deficiency

(649) ACTH deficiency is potentially a life-threatening condition. Once identified using the insulin tolerance test, life-long hydrocortisone replacement is required and increased doses may be necessary for surgery or intercurrent illness.

Management of radiation-induced damage to gonadotropin secretion

(650) Gonadotropin deficiency increases with time following cranial irradiation of >50 Gy (in 2-Gy fractions) with a cumulative incidence of 20–50% reported among long-term survivors of non-pituitary brain tumours. Cranial irradiation of pituitary-related tumours is associated with gonadotropin deficiency, reported in 33% and 66% of 5-year survivors following 20 and 35–40 Gy (in 2-Gy fractions), respectively (Littley et al., 1989). This may manifest as a spectrum of abnormalities from subclinical biochemical insufficiency on GnRH testing to clinically detectable hypogonadism. Basal LH/FSH levels are usually normal or low with diminished sex hormone concentrations, and GnRH testing demonstrates a delayed peak gonadotropin response and/or a delayed decline indicating hypothalamic damage. Pituitary damage is indicated by a blunted response, and a mixed response may indicate damage at both sites. It may be possible to restore pituitary function, and thus differentiate between primary and secondary pituitary atrophy, by repeated intermittent infusion of GnRH (Yoshimoto et al., 1975). In this situation, GnRH treatment would enable restoration of gonadal function (Hall et al., 1994).

(651) All children should undergo regular assessment of pubertal status and Tanner staging as appropriately indicated by age and clinical examination (Scottish Intercollegiate Guidelines Network, 2004). In postpubertal males, testicular volume <12 ml strongly correlates with impaired spermatogenesis. Hormone assessments of serum FSH/LH, testosterone, and oestradiol in males and females, respectively, should also be performed routinely. Inhibin B strongly correlates with Sertoli cell function and spermatogenesis in males, and AMH (Anti-Mullerian Hormone) in females reflecting primordial follicle reserve.

(652) Precocious puberty is defined as the development of secondary sexual characteristics at an age that is >2 standard deviations earlier than the population mean; generally accepted as <8 years for girls and <9 years for boys. Low-dose cranial irradiation with doses of ≤ 24 Gy (in 2-Gy fractions), as was historically used for CNS-directed treatment of ALL, is associated with precocious puberty, predominantly affecting girls (Leiper et al., 1987). On the other hand, with cranial irradiation doses of 25–50 Gy (in 2-Gy fractions), there is no gender difference in the incidence of precocious puberty (Ogilvy-Stuart et al., 1994). The clinical impact of premature activation of the gonadal axis is compounded by the co-existence of GH insufficiency, resulting in attenuation of the pubertal growth spurt. GnRH analogues may be used to arrest pubertal progression and to maximise the benefit of GH replacement therapy.

3.3.11. Nervous system

Anti-inflammatory and anticoagulant agents

(653) There are anecdotal clinical reports of a beneficial effect of steroids to treat delayed radionecrosis of the brain (Shaw and Bates, 1984; Soffietti et al., 1985); this probably results from restoration of the endothelial junctions within the cerebral micro-vasculature and consequent reduction in cerebral oedema. There is also anecdotal evidence for beneficial effects of anticoagulant therapy in patients with late brain necrosis, myelopathy, or plexopathy who were unresponsive to dexamethasone (Glantz et al., 1994).

(654) Daily injections of dexamethasone have been shown to prevent early increases in vascular permeability after left hemisphere irradiation of rabbits with a single dose of 30 Gy (Blomstrand et al., 1975), and to significantly reduce oedema at 1 week and 1 month after interstitial irradiation of monkey brain (Tada et al., 1997). There is also some anecdotal evidence that the steroidal anti-inflammatory drug meclufenamate may prevent the development of oedema and hydrocephalus in monkeys after 20 Gy (Halpern et al., 1984). However, dexamethasone for 24 days after whole-brain irradiation or interstitial focal brain irradiation of monkeys did not have any effect on subsequent long-term behavioural changes, motor impairment, or radionecrosis (Martins et al., 1979; Tada et al., 1997).

(655) High-dose dexamethasone reduced capillary permeability and delayed the onset of paraplegia when given to symptomatic rats after irradiation of the spinal cord with 30 Gy (Delattre et al., 1988). In contrast, long-term administration of very low doses of dexamethasone has been shown to exacerbate the severity of radiation myelopathy in rats (Geraci et al., 1993).

(656) There is recent interest in the use of anti-inflammatory peroxisomal proliferator-activated receptor (PPAR) agonists to inhibit inflammatory brain damage after whole-brain irradiation. In-vitro studies have demonstrated a significant inhibition of radiation-induced inflammatory responses in microglial cells by treatment with PPAR α agonists (Ramanan et al., 2008). In-vivo studies in rats have shown that a PPAR γ agonist given before and for 4 or 54 weeks after whole-brain irradiation prevented the cognitive impairment induced by 40–45 Gy (given in eight or nine

fractions) (Zhao et al., 2007). Since these drugs are relatively non-toxic and are already in clinical use as anti-diabetic agents, they appear to be good candidates for testing in clinical trials for cancer patients receiving brain irradiation.

ACE inhibitors and AII receptor antagonists

(657) The brain has a functioning renin–angiotensin system that is involved in modulation of the BBB, as well as memory and cognition (Robbins and Diz, 2006). Angiotensin receptor antagonists have been shown to improve cognitive function in patients with hypertension, independent of reductions in blood pressure (Tedesco et al., 2002). In experimental rat models, chronic administration of an ACE inhibitor reduced the severity of optic neuropathy after stereotactic brain irradiation with 30 Gy (Kim et al., 2004). Chronic administration of an angiotensin receptor antagonist also prevented or reduced cognitive impairment of rats after fractionated whole-brain irradiation (40 Gy in eight fractions). When the drug was given continuously from 3 days before irradiation, it completely abolished the radiation-induced cognitive impairment at 6 months and 1 year. Drug given before, during, and for 5 weeks after irradiation significantly reduced but did not eliminate the cognitive impairment (Robbins et al., 2009).

Thiols and radical scavengers

(658) Intrathecal administration of the thiol radical scavenger amifostine before spinal cord irradiation of rats resulted in significant increases in median time to myelopathy, with an estimated DMF of 1.3 (Spence et al., 1986).

Growth factors

(659) Experimental studies have shown that growth factors including IGF-1, platelet-derived growth factor, or bFGF given for a few days prior to irradiation of the spinal cord can increase the latent time to development of necrosis. When intrathecal IGF was combined with amifostine, this led to an increase in radiation tolerance by approximately 7% (Nieder et al., 2005, 2007). Part of the protective effect of bFGF could be due to inhibition of endothelial cell apoptosis within 1 day after irradiation, as has been shown in irradiated mouse spinal cord (Pena et al., 2000).

(660) Hypoxia and increased VEGF expression are associated with breakdown of the BBB preceding white matter necrosis and paralysis after spinal cord irradiation (Li et al., 2001). This observation has led to clinical trials using bevacizumab, a monoclonal antibody against VEGF, after brain irradiation. Significant reductions in brain oedema have been reported, albeit in small numbers of patients (Gonzalez et al., 2007; Torcuator et al., 2009).

Other modifiers

(661) The PUFA, gamma linolenic acid (GLA) was shown to be effective in reducing injury in irradiated pig spinal cord, with a 10% increase in tolerance dose (Hopewell et al., 1994b). GLA was subsequently tested in conjunction with radiosurgery for patients with large arteriovenous malformations (Sims and Plowman, 2001). The GLA-treated group had significantly fewer permanent complications, but they

also had less effective obliteration of the lesions; therefore, there was no overall therapeutic gain.

(662) Vasoactive drugs such as dipyridamole (increases blood flow and reduces thrombosis) and desferrioxane combined with a low iron diet (reduces reperfusion injury) given from 17 weeks after irradiation were shown to delay the onset of ataxia and increase spinal cord tolerance by approximately 10% in rats (Hornsey et al., 1990).

Stem cells

(663) Rezvani et al. (2001) showed that transplantation of neural progenitors could be used to ameliorate radiation-induced myelopathy in rats. Immortalised neural stem cells were injected directly into the spinal cord at 3 months after irradiation. Paralysis-free survival improved significantly in the injected rats, but the fate of the donor cells was not traced and hence the biological mechanisms for the effect are not yet clear.

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4. THRESHOLD DOSES IN RELATION TO RADIOSENSITIVITY OF ORGANS AND TISSUES

4.1. Introduction

(664) The recommended dose limits for tissue reactions (deterministic effects) are based on threshold doses for morbidity in specific organ systems and for mortality. These threshold doses are derived from past events and experiences, and many of the values have remained unchanged because of the lack of new evidence which might have indicated the need for change. In contrast, the management of some radiation-induced tissue reactions has gradually improved over many years, and therefore there is a need to consider the magnitude of change in dose thresholds associated with the use of new treatments and management of the reactions. In addition, epidemiological studies of populations exposed in various situations have provided more information on the risk of morbidity and mortality from non-cancer diseases.

(665) Recently, a survey of organ tolerances to fractionated radiotherapy treatments has been completed (Marks et al., 2010). This information is summarised in Table 4.1, and helps to formulate threshold doses for such dose schedules which are generally comprised of daily 2-Gy fractions. However, it must be recognised that incidences of injury in this table are often much higher than 1% and hence extrapolations are needed, and the assessments are often made at 5 years after treatment and not at the longer times which are necessary for protection purposes when tolerance doses may be less because of progression of injury.

(666) In the 2007 Recommendations (ICRP, 2007), it was stated that two organ systems required further special consideration. Firstly, much evidence has been accruing in recent years regarding radiation-induced eye cataracts, strongly suggesting that threshold doses should be much reduced from those recommended previously. Secondly, evidence from different sources indicates that radiation-induced circulatory disease may be occurring at much lower doses than had previously been appreciated, and the cardiovascular and cerebrovascular system may need to be included in the list of organs at risk from low doses. Both of these organ systems have received detailed attention in the present report.

(667) This report has not considered tissue reactions after high-LET irradiations. These were described in detail in *Publication 58* (ICRP, 1990) and included in ICRP *Publication 92* (ICRP, 2003). Reports from other organisations have also been published for protection purposes (e.g. NCRP, 1990), and for particular applications such as radiotherapy (e.g. IAEA, 2008).

4.2. Haematopoietic and immune systems

(668) Acute threshold doses of approximately 0.5 Gy, and chronic dose rates of 0.4 Gy/year, remain as recommended values for depression of haematopoiesis (Section 2.1). Also, for mortality, the threshold values of approximately 1 Gy acute dose without medical care and 2–3 Gy with good medical care are unchanged from previous ICRP values. There are no new confirmatory data.

Table 4.1. Approximate dose/volume/outcome data for whole-organ (unless otherwise stated) irradiation with conventional fractionation (1.8–2.0 Gy/fraction). All data are estimated from the literature summarised in the QUANTEC reviews as summarised in Table 1 from Marks et al. (2010).

Organ	Endpoint	Dose (Gy) or dose/volume parameters	Rate (%)
Brain	Necrosis	$D_{max} < 60$	<3
		$D_{max} = 72$	5
Brain stem	Neuropathy or necrosis	$D_{max} < 54$	<5
Optic nerve/chiasm	Neuropathy	$D_{max} < 55$	<3
		$D_{max} = 55-60$	3–7
Spinal cord*	Myelopathy	$D_{max} = 50$	0.2
		$D_{max} = 60$	6
Cochlea	Hearing loss	$D_{mean} < 45$	<30
Parotid glands bilateral	Salivary function <25%	$D_{mean} < 25$	<20
Pharynx	Dysphagia and aspiration	$D_{mean} < 50$	<20
Larynx	Vocal dysfunction	$D_{max} < 66^\dagger$	<20
		$D_{mean} < 44$	
Lung	Pneumonitis	$V_{50} < 27\%$	
		$V_{20} < 30\%$	<20
		$D_{mean} = 7$	5
Oesophagus	Oesophagitis Grade 3	$D_{mean} = 13$	10
		$D_{mean} < 34$	5–20
		$V_{35} < 50\%$	<30
Heart	Pericarditis	$D_{mean} < 26$	<15
		$V_{30} < 46\%$	<1
		$V_{25} < 10\%$	
Liver [‡]	Radiation-induced liver disease	$D_{mean} < 30-32$	<5
Kidney	Renal dysfunction	$D_{mean} < 15-18$	<5
		$V_{12} < 55\%$	
		$V_{20} < 32\%$	
Stomach	Ulceration	$D_{100} < 45$	<7
Small bowel	Grade 3 acute toxicity	$V_{45} < 195$ cc	<10
Rectum	Grade 2 late toxicity	$V_{50} < 50\%$	<15
		Grade 3 late toxicity	<10
Bladder	Grade 3 late RTOG toxicity	$D_{max} < 65$	<6
Penile bulb	Erectile dysfunction	$D_{60-70} < 70$	<55

D_{max} , maximum dose to organ; D_{mean} , mean dose to organ; D_x , minimum dose to 'hottest' $x\%$ of organ; V_x , volume of organ exposed to dose x ; RTOG, radiation therapy oncology group.

* Partial-organ irradiation, including full cord cross-section.

† With chemotherapy

‡ Excluding patients with pre-existing liver disease.

(669) Bone marrow is noted for its small dose fractionation sparing effect, but protraction of dose allows marked repopulation. A summary of small numbers of individuals exposed to protracted doses in various accidents with minimal medical attention showed survival in all cases, at least in the short term, after estimated marrow doses of 4–8 Gy in 1 week or 10–14 Gy accumulated over 1–3 months (UNSCEAR, 1988).

(670) Medical management is an essential component of successful recovery from the haematopoietic syndrome following potentially lethal radiation exposure.

Growth factor administration can increase survival rates in victims of radiation accidents. However, the marked heterogeneity and uncontrolled nature of the radiation exposure and the insufficient numbers of people available for analysis prevent well-defined estimates of survival benefit. In dogs, threshold doses can be approximately doubled by the use of good clinical support and growth factors (MacVittie et al., 1991), demonstrating the potential of these approaches for exposed humans.

4.3. Digestive system

(671) The acute threshold dose for early mortality at 6–9 days after intestinal irradiation is considered to remain at 6 Gy, and good medical care is expected to increase this value. The corresponding value for fractionated doses can be deduced from the response of patients receiving radiotherapy, which includes more recent data (Section 2.2).

(672) The incidence and severity of delayed intestinal radiation toxicity depends on radiation dose, volume of bowel irradiated, fractionation schedule, concomitant chemotherapy, and comorbidities and other patient factors. The threshold doses for late injury after irradiation of specific parts of the digestive system come from the response of radiotherapy patients. These dose levels show the greater sensitivity of the parotids and the liver, for example, compared with the lower sensitivity of the larynx and rectum. Tables containing information about dose–volume effects in various organs of the digestive tract have been published by the QUANTEC group (Deasy et al., 2010; Kavanagh et al., 2010; Michalski et al., 2010; Pan et al., 2010; Rancati et al., 2010; Werner-Wasik et al., 2010).

(673) There are no well-established ways of mitigating intestinal injury after irradiation (Section 3.3.2). The most promising enterotrophic strategies with the potential to protect the intestine from radiation injury include some cytokines, gastrointestinal peptide hormones, and a variety of nutrients. For example, preclinical studies show that reducing intraluminal pancreatic secretions with a synthetic somatostatin receptor analogue, octreotide, markedly ameliorates both early and delayed radiation enteropathy, and this is beginning to have clinical application.

4.4. Reproductive system

(674) The threshold doses for males for acute, fractionated/protracted, and chronic exposures, and the bases for these doses, remain virtually the same as recommended in the last review of deterministic effects by ICRP (ICRP, 1984). There is a trend for the threshold dose to be less for fractionated/protracted exposures compared with single exposures (reverse fractionation effect). Hormonal manipulation of spermatogenic recovery has been investigated in humans, but with little conclusive improvement. In animals, several biological response modifiers have been investigated including hormonal manipulation, antioxidants, radical scavengers, and natural compounds. Various degrees of benefit have been reported that are species and

endpoint specific. At the present time, there is no over-riding conclusion that would favour one compound over others for medical application (Section 3.3.3).

(675) The threshold doses for females for acute, fractionated/protracted, and chronic exposures remain the same as previously recommended by ICRP (ICRP, 1984). It is noted that sensitivity increases with age because of the decline in the size of the oocyte pool with increasing age (Section 2.3.3). Regarding protection, although numerous studies in female patients undergoing chemotherapy (and some radiotherapy) indicated that GnRH analogues might be protective of ovarian function, none of these studies were prospective randomised clinical trials and thus the evidence was inconclusive (Meistrich and Shetty, 2008). Animal studies using some hormonal approaches, anti-apoptotic agents, or radical scavengers have produced some evidence of protection, but none has reached clinical application to date (Section 3.3.3).

4.5. Skin

(676) The radiation response of the skin was documented extensively in *Publication 59* (ICRP, 1991) and summarised in *Publication 85* (ICRP, 2000). The salient features of response have not changed over the years, and they are re-stated in Section 2.4 of the present report. This includes threshold doses for the different early and late reactions, skin area and dose fractionation effects, and the effects of inhomogeneous doses to epidermis and dermis.

(677) Protective agents given before irradiation of animal skin systems include radical scavengers, prostaglandins, and nitroxides. In recent years, there have been studies using a variety of mitigating agents in attempts to reduce early and late skin reactions after irradiation in human and animal systems. In humans, the most successful agents for reducing early reactions are anti-inflammatory compounds. In animal systems, some anti-inflammatory agents and PUFAs have shown promise for reducing early reactions. For reducing late reactions, SOD, FGF, captopril, PUFAs, α -tocopherol, and inhibition of TGF- β signalling have shown some promise in both human and animal systems. The DMF in animal systems showing some effect is generally around 1.1–1.2, with a maximum reported among all studies of around 1.5.

4.6. Cardiovascular and cerebrovascular systems

(678) Circulatory disease has not previously been listed by ICRP as a health hazard from radiation exposures to organs and tissues, because it is only in the last few years that there has been greater consolidation of the evidence on this topic. This includes heart disease arising >10 years after irradiation from atomic bombs or after the Chernobyl accident, or after irradiation of a part of the heart during radiotherapy for breast cancer, peptic ulcer, or Hodgkin's lymphoma. There are many other radiation scenarios, medically and occupationally, where populations have been exposed to lower heart doses (UNSCEAR, 2006), but generally these have not been as informative as the radiotherapy exposures where heart doses can be assessed more accurately. There is no clear pattern across studies regarding whether or not the

ERR for cardiovascular disease is greater than that for stroke or cerebrovascular disease (Section 2.5).

(679) Schultz-Hector and Trott (2007) concluded that the atomic bomb and radiotherapy survivor data could be brought into reasonable agreement if the fractionated radiotherapy doses to (a part of) the heart were converted into iso-effective single doses, averaged over the whole heart, allowing for the acknowledged high sensitivity of the heart to dose fractionation. This composite analysis indicated a small single-dose threshold of around 1 Gy. A recent updated analysis of the atomic bomb survivor data (Shimizu et al., 2010) estimated the threshold dose (weighted colon dose) for heart disease to be 0 Gy with an upper 95% confidence limit of 0.5 Gy. However, over the range of 0–0.5 Gy, the dose response was not statistically significant, indicating that the low-dose data are weak. For stroke, the estimated threshold dose was 0.5 Gy, with an upper 95% confidence limit of 2 Gy.

(680) Recent reviews of epidemiological studies of populations medically, occupationally, or environmentally exposed to relatively low-dose radiation showed that there was substantial heterogeneity in the association between radiation exposure and circulatory disease, with respect to the risk per unit radiation dose, possibly resulting from confounding factors or bias (Little et al., 2008; Little et al., 2010). This analysis indicated that heterogeneity was reduced, but remained significant, when adjustments were made for fractionation of exposure and when examining heart disease and stroke separately. The epidemiological evidence for an effect of moderate and low doses (i.e. <5 Gy) was viewed by Little et al. (2010) as being suggestive rather than persuasive, and no dose threshold analysis was made.

(681) In the introduction to this report, the term ‘practical’ threshold dose was defined as denoting the amount of radiation that is required to cause a specific, observable effect in only 1% of individuals exposed to radiation. In the case of circulatory disease, it is difficult to distinguish circulatory disease associated with radiation exposure from another causal agent, because of the high natural baseline mortality incidence of 30–50% in most developed countries. Furthermore, it is unclear whether there is a dose below which the risk of circulatory disease is not increased and, if so, what this dose might be. Nevertheless, based on the epidemiological findings, it is possible to estimate the magnitude of dose at which circulatory disease might be induced among 1% of exposed individuals.

(682) Whilst the estimates of the ERR/Gy in Table 2.3, based on a linear dose–response analysis, vary between studies and between specific types of circulatory disease, an ERR/Gy of around 0.1 would seem to be a reasonable summary value, particularly in the case of the atomic bomb study. A recent report (Table 8 in AGIR, 2010), calculating aggregate risks from many studies, estimated an ERR/Gy of 0.10 (95% CI 0.07–0.13) for morbidity and 0.08 (95% CI 0.04–0.12) for mortality from circulatory disease taken as a whole. If an ERR/Gy of this magnitude were to apply at doses in the range of 0.5 Gy, and the baseline incidence is 30–50%, this would imply that a dose of 0.5 Gy might increase mortality from circulatory disease by approximately $0.08 \times 0.5 \times (30-50)\% = 1.2-2\%$. Given that not all cases of circulatory disease are fatal, the corresponding percentage for morbidity would be expected to be greater. Overall, and subject to the assumptions outlined here, a dose of around

0.5 Gy might lead to approximately 1% of exposed individuals developing circulatory disease.

(683) It is unclear from Table 2.4 whether the ERR/Gy for cardiovascular disease is greater than that for cerebrovascular disease. In a recent report (Table 8 in AGIR, 2010), the aggregate ERR/Gy from many appropriate studies was estimated to be 0.09 (95% CI 0.05–0.12) for cardiovascular disease and 0.21 (95% CI 0.16–0.27) for cerebrovascular disease. However, around a potential threshold dose of 0.5 Gy, this difference is uncertain. On the basis that the baseline risk for cardiovascular disease (e.g. around one in six deaths in the UK – AGIR, 2010) is greater than that for cerebrovascular disease (around one in nine of deaths in the UK – AGIR, 2010), then as the ERR/Gy may be greater for cerebrovascular disease than for cardiovascular disease, a ‘threshold dose’ of 0.5 Gy is proposed here for both cardiovascular disease and cerebrovascular disease on the basis that this dose might lead to approximately 1% of exposed individuals developing each disease in question. Nevertheless, there are notable uncertainties in determining risks of these diseases at this level of dose.

(684) Regarding partial-body exposure, it is assumed that the risk depends on the dose in the target tissue or organ. However, it is not known what part of the heart or the cerebrovascular system is the most sensitive and critical regarding risk. Hence for the present purposes, the mean dose is assumed to be appropriate, and future research may elucidate this further.

(685) It is unclear whether or not the ERR/Gy is the same for acute, fractionated, and chronic exposures. Similar threshold doses would be expected in these three conditions if the risk at doses up to the threshold dose were governed by single-hit irreparable injury, with no split-dose repair, slow repair, or cell repopulation effect involved at these very low dose levels. However, the problem for the present purpose is the difficulty of determining the threshold dose to a good degree of accuracy in different human exposure scenarios, and the much discussed likelihood of the mechanism of circulatory disease being different at high vs low doses. If the mechanisms are different, it is probably fortuitous that threshold doses are considered similar for acute, fractionated, or chronic exposures, and statistical uncertainties are reflected in this choice. For the purposes of the present assessment, the ERR/Gy and hence the ‘threshold dose’ is taken to be the same for all three types of exposure, i.e. around 0.5 Gy. Future studies may elucidate this further.

(686) Although some of the older radiotherapy data for fractionated doses could be brought into reasonable agreement with the atomic bomb data for single doses, after correcting for dose fractionation effects, other radiotherapy data have indicated much higher threshold doses. This is probably due, in part, to quoting in-field doses rather than average heart doses which would be lower, and the shorter follow-up times of approximately 15 years in those cases. In the present context of protection, it is the threshold doses which apply for very long follow-up times that are the most relevant for workers and the public, as is the case for the atomic bomb survivors (40–50 years follow-up) and the peptic ulcer study (22.5 and 27.5 years). The radiotherapy data generally apply for shorter follow-up times because of competing causes of

death when the risks of circulatory disease mortality are lower. However, several recent radiotherapy studies now have 30 years of follow-up.

(687) For perspective, the estimated risk of fatal cancer associated with exposure to a whole-body dose of 0.5 Gy (low LET) would be 2%, whether delivered acutely or spread evenly over an entire working life, assuming a nominal risk coefficient for workers of 4%/Sv. For a population of all ages with a cumulative whole-body dose of 0.5 Gy (low LET) arising from chronic exposure, assuming a nominal risk coefficient of 5% per Sv, the estimated fatal cancer risk would be 2.5%. These values are of a similar order to those assumed here for circulatory disease. However, it should be stressed that the magnitude and form of any circulatory disease risk associated with doses of the order of 0.5 Gy and below remain particularly uncertain.

(688) The mechanisms of radiation-induced heart damage include inflammatory processes, in particular after low doses. After higher doses, there is a progressive reduction in the number of patent capillaries eventually leading to ischaemia, myocardial cell death and fibrosis, accelerated atherosclerosis in major blood vessels, decreased cardiac function, and fatal congestive heart failure. There are no known mitigators of radiation-induced cardiovascular disease. Possibilities are statins, generally used to treat heart conditions, and glutamine supplementation, and laboratory research is further investigating the benefits of using stem cell transplantation or stem cell products.

4.7. Eye

(689) A recent review of epidemiological studies of radiation-induced cataracts (Ainsbury et al., 2009) included eight studies published since 1999 that estimated ORs or RRs for cataract development at 1 Gy or 1 Sv, or comparisons of exposed and unexposed groups (Fig. 4.1) (see also Table 4.2). These various studies on clinical or occupational cohorts, atomic bomb survivors, Chernobyl clean-up workers, and pilots consistently showed an elevated risk at 1 Gy (Section 2.6). It should also be noted that the majority of studies with cancer patients receiving proton therapy instead of conventional photon therapy have concluded that late effects, including cataracts, induced by protons are nearly equivalent to what one would expect from equivalent photon doses. RBE values are around 1.0, except near the very end of the stopping Bragg peak (Blakely and Chang, 2004).

(690) Formal estimates of acute threshold doses (Table 4.3) have been made in two studies on atomic bomb survivors (Nakashima et al., 2006; Neriishi et al., 2007). These provided threshold doses of 0.1–0.7 Gy, with 90–95% CI including 0 Gy. Estimates of threshold doses for protracted exposures were calculated from the data for Chernobyl survivors (Worgul et al., 2007). These estimates ranged between 0.34 and 0.50 Gy (95% CI 0.17–0.69 Gy). There was no dependence of threshold dose on stage or site of the cataract. Although the large majority of cataracts in the Nakashima and Worgul studies (Table 4.3) were only small Stage 1 cataracts, those in the Neriishi studies were surgically removed cataracts. A fi-

Table 4.2. Summary of results of many of the studies of radiation-induced lens changes.

Author	No. of subjects	Age at exposure (years)	Follow-up time (years)	Dose range or average (Gy)*	Fractions	Results	Comments
<i>Treatments</i>							
Cogan and Dreisler (1953)	40	15–70	7 (1–14)	0.23–24	1– <i>n</i>	5 cataracts, none <5 Gy	Small case series, short follow-up
Merriam and Focht (1957)	100	0.9–84	5–9	0.25–69	1– <i>n</i>	All cataracts >2 Gy or fractions >5 Gy	Clinical series, <i>n</i> = 33 at <200 rad, short follow-up
Qvist and Zachau-Christiansen (1959)	56	Infants	>20–40	>1	1–15	4 cataracts at >6.9 Gy	Small study
Albert et al. (1968)	234	8 (1–14)	10	0.5	5 (over a few minutes)	13 opacities	Small study
Wilde and Sjostrand (1997)	20	0.2–1	30–46	1–11 ²²⁶ Ra	1 (1.5–3 h)	Opacities vs dose	Small study
Hall et al. (1999)	484	0.4 (0–1.3)	46	0.4 (0–8.4) ²²⁶ Ra	2 (1–14)	Cataracts vs dose	Cortical not nuclear vs dose
<i>Atomic bomb survivors</i>							
Cogan et al. (1950)	1000	All	4	NA	1	Some opacities	Screening study
Choshi et al. (1983)	2385	All	33–35	>1	1	Increased opacities	No dose–response relationship estimated
Otake et al. (1996)	~2000	All	18–19	NA	1	Various opacities/ cataracts	Screening study

Table 4.2. (continued)

Author	No. of subjects	Age at exposure (years)	Follow-up time (years)	Dose range or average (Gy)*	Fractions	Results	Comments
Nakashima et al. (2006)	>700	~8.8	55–57	0.52 (0–>2) Sv	1	Threshold 0.6–0.7 Sv	Increased opacities
Neriishi et al. (2007)	3761	0–>20	55–57	0–>3	1	Threshold 0.1 (0–0.8) Gy	12.7% cataract surgery
<i>Accidents, residents</i>							
Day et al. (1995)	991	0–12	5–7	0.030 Sv	Protracted	Some opacities	Chernobyl residents
Nadejina et al. (2002)	41	~35	14	0.2–3.2	Protracted	Cataracts at 3.2 Gy	Small study
Worgul et al. (2007)	8607	Adults	12–14	0–1	Protracted	Opacities	Chernobyl clean-up workers
Hsieh et al. (2010)	73	<20	4.7	~0.200 Sv	~7 years	Some opacities	Residential exposure
<i>Workers</i>							
Junk et al. (2004)	59	NA	5–36	NA	5–36 years	Cataracts at long times	Chronic exposure
Shang and Fu (2007)	584	20–57	0.3–35	NA	0.4–35 years	Opacities at long times	Chronic exposure
Chodick et al. (2008)	35,705	Workers	~19	0.005–0.06	6–13 years	Cataracts at higher dose	Radiological technologists self-reporting
Kleiman et al. (2009)	78	Interventional cardiologists	1–40	NA	Chronic	Some opacities	Doses unknown

NA, not available; RERF, Radiation Effects Research Foundation.

See Annex A for further details. Information courtesy of Dr. R.E. Shore, R.E.R.F. (Radiation Effects Research Foundation), Hiroshima, Japan.

* Sv where stated; *n* = number of fractions.

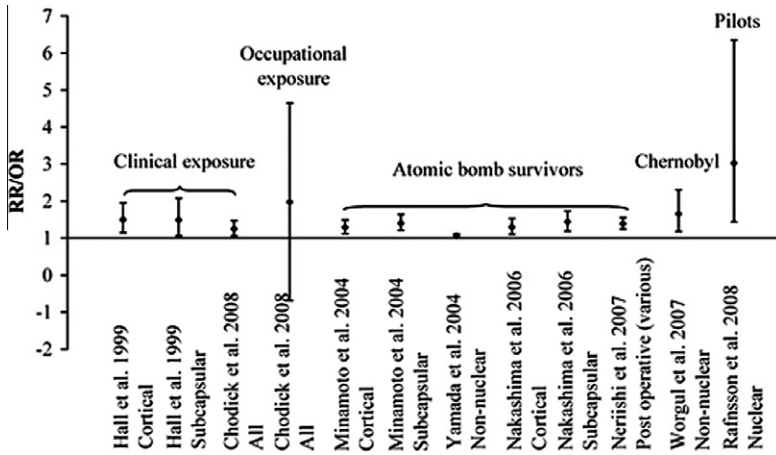


Fig. 4.1. Odds ratio (OR) or relative risk (RR) for cataract development, either at 1 Gy or 1 Sv, or from comparisons of exposed and unexposed groups in various studies (Ainsbury et al., 2009).

Table 4.3. Recent epidemiological studies of cataract formation where formal estimates of threshold doses were made.

Study	Cataract type	Threshold dose	Confidence intervals	Reference
Atomic bomb survivors (acute exposure)	Cortical cataract	0.6 Sv	90%: <0–1.2 Sv	Nakashima et al. (2006)
	Posterior subcapsular opacity	0.7 Sv	90%: <0–2.8 Sv	
Atomic bomb survivors (acute exposure)	Postoperative cataract	0.1 Gy	95%: <0–0.8 Gy	Neriishi et al. (2007)
Chernobyl clean-up workers (fractionated protracted exposure)	Stage 1–5 cataract	0.50 Gy	95%: 0.17–0.65 Gy	Worgul et al. (2007)
	Stage 1 cataract	0.34 Gy	95%: 0.19–0.68 Gy	
	Stage 1 non-nuclear cataract	0.50 Gy	95%: 0.17–0.69 Gy	
	Stage 1 superficial cortical cataract	0.34 Gy	95%: 0.18–0.51 Gy	
	Stage 1 posterior subcapsular cataract	0.35 Gy	95%: 0.19–0.66 Gy	

nal analysis of the latter that included age, gender, city, and history of diabetes as potential confounding variables estimated a 33% increase in cataract surgery risk at 1 Gy (RR 1.33, 95% CI 1.20–1.47). A dose-threshold analysis found a best estimate of 0.4 Gy (95% CI 0–0.8) (reported in Blakely et al., 2010). This provides the strongest evidence to date that vision-impairing cataracts are in excess at doses of <1 Sv. In addition, those studies showed a non-significant decreasing radiation risk by age at exposure on the excess absolute risk scale. Regarding chronic irradiation, there have been studies of diagnostic radiation technologists, commercial pilots and astronauts, and residents of radioactive buildings in

Taiwan. These studies are not generally as informative about threshold doses, but all of them are consistent in showing some degree of risk at low doses. The protraction of doses in occupationally and environmentally exposed cohorts does not appear to reduce risk to a significant extent.

(691) The precise mechanism of radiation cataractogenesis is not known, but genomic damage resulting in altered cell division, transcription, and/or abnormal lens fibre cell differentiation is considered to be the salient injury, rather than cell killing. One theory is that aberrantly dividing and/or differentiating cells in the pre-equatorial region of the lens epithelium migrate, predominately to the lens posterior pole, where they become opaque lens fibres. Radiation damage to single lens epithelial or fibre cells probably results in small localised changes in lens transparency. It has been suggested that accumulation and coalescence of these micro-opacities results in populations of damaged lens fibre cells that form larger lens defects, eventually resulting in clinical opacity. It has also been suggested that radiation cataract formation is likely to be dependent on survival and potential division and/or differentiation of lens epithelial cells with compromised genomes. Thus, radiation-induced unrepaired DNA damage in such dividing and differentiating lens epithelial cells may be the crucial first step in cataractogenesis. Lenses containing cells with impaired ability to recognise and repair such damage are probably at increased risk for cataractogenesis, and heterozygosity for genes involved in cell-cycle checkpoint control, DNA damage recognition, or DNA repair might also contribute to this phenomenon.

(692) There is no direct mechanistic evidence that a single damaged cell can give rise to a cataract, which would be the hallmark of a stochastic effect with zero threshold. However, there is evidence of the importance of cell division and proliferation in the formation of cataracts. In the lens epithelium of patients with cataracts, an increased frequency of micronuclei (a marker of impaired cell division) has been reported, and in animals, it has been shown that radiation cataracts will not form if epithelial cell division is totally inhibited or if the dividing epithelial cells are shielded from radiation exposure. It can be speculated that radiation cataract formation could be explained by initial damage to a single progenitor epithelial cell in the lens which, upon cell division and differentiation, results in groups of defective lens fibre cells. Future research may elucidate the true mechanism of cataract formation.

(693) In *Publication 103* (ICRP, 2007), the threshold doses for visual-impairing cataracts were given as 5 Gy for acute exposures and >8 Gy for highly fractionated or protracted exposures. These values were unchanged from the 1990 Recommendations (ICRP, 1991). Lower threshold doses were quoted for detectable lens opacities of 0.5–2 Gy for acute exposures and 5 Gy for highly fractionated or protracted exposures. The data were derived from earlier studies on the atomic bomb survivors and radiotherapy patients (ICRP, 1984). These early studies of radiation cataract generally had short follow-up periods, failed to consider the increasing latency period as dose decreases, did not have sufficient sensitivity in detecting early lens changes, and had relatively few subjects with doses below a few Gy (Section 2.6.1). Also, there is considerable heterogeneity in the approaches used to document radiation-associated

Table 4.4. Estimates of the threshold doses. * for approximately 1% incidence of morbidity in tissues and organs in adults exposed to acute, fractionated or protracted, and chronic irradiation.

Effect	Organ/tissue	Time to develop effect	Acute exposure (Gy)	Highly fractionated (2-Gy fractions) or equivalent protracted exposures (Gy) [†]	Annual (chronic) dose rate for many years (Gy/year)
Temporary sterility	Testes	3–9 weeks	~0.1	NA	0.4
Permanent sterility	Testes	3 weeks	~6	<6	2.0
Permanent sterility	Ovaries	<1 week	~3	6.0	>0.2
Depression of haematopoiesis	Bone marrow	3–7 days	~0.5	~10–14	>0.4
Xerostomia	Salivary glands	1 week	NA	<20	NA
Dysphagia, stricture	Oesophagus	3–8 months	NA	55	NA
Dyspepsia, ulceration	Stomach	2 years	NA	50	NA
Stricture	Small intestine	1.5 years	NA	45	NA
Stricture	Colon	2 years	NA	45	NA
Anorectal dysfunction	Rectum	1 year	NA	60	NA
Hepatomegaly, ascites	Liver	2 weeks–3 months	NA	<30–32	NA
Main phase of skin reddening	Skin (large areas)	1–4 weeks	<3–6	30	NA
Skin burns	Skin (large areas)	2–3 weeks	5–10	35	NA
Temporary hair loss	Skin	2–3 weeks	~4	NA	NA
Late atrophy	Skin (large areas)	>1 year	10	40	NA
Telangiectasia at 5 years	Skin (large areas)	>1 year	10	40	NA
Cataract (visual impairment)	Eye	>20 years	~0.5	~0.5	~0.5 divided by years duration [‡]

Table 4.4. (continued)

Effect	Organ/tissue	Time to develop effect	Acute exposure (Gy)	Highly fractionated (2-Gy fractions) or equivalent protracted exposures (Gy) [†]	Annual (chronic) dose rate for many years (Gy/year)
Acute pneumonitis	Lung	1–3 months	6–7	18	NA
Oedema	Larynx	4–5 months	NA	70	NA
Renal failure	Kidney	>1 year	7–8	18	NA
Fibrosis/necrosis	Bladder	>6 months	15	55	NA
Stricture	Ureters	>6 months	NA	55–60	NA
Fracture	Adult bone	>1 year	NA	50	NA
Fracture	Growing bone	<1 year	NA	25	NA
	Muscle	Several years	NA	55	NA
Endocrine dysfunction	Thyroid	>10 years	NA	>18	NA
Endocrine dysfunction	Pituitary	>10 years	NA	≤10	NA
Paralysis	Spinal cord	>6 months	NA	55	NA
Necrosis	Brain	>1 year	NA	55–60	NA
Cognitive defects	Brain	Several years	1–2	<20	NA
Cognitive defects infants <18 months	Brain	Several years	0.1–0.2	NA	NA

NA, not available.

* Most values rounded to nearest Gy; ranges indicate area dependence for skin and differing medical support for bone marrow.

† Derived in most cases from fractionated radiotherapeutic exposures, generally using 2-Gy fractions. For other fraction sizes, the following formula can be used, where D is total dose (number of fractions multiplied by d), d is dose per fraction (2 Gy in the case of D_1 , and new value of d in the case of D_2), and the ratio α/β can be found in the appropriate section of this report: $D_1[1 + 2/(\alpha/\beta)] = D_2[1 + d_2/(\alpha/\beta)]$. Protracted doses at a low dose rate of around 1 cGy/min are approximately iso-effective to doses delivered in 2-Gy fractions at high dose rate for some tissues, but this equivalence is dependent on the repair half-time of the particular tissue. Further details can be found in Joiner and Bentzen (2009), Bentzen and Joiner (2009), and Van der Kogel (2009).

‡ The values quoted for the lens assume the same incidence of injury irrespective of the acute or chronic nature of the exposure, with >20 years follow-up. It is emphasised that great uncertainty is attached to these values.

Table 4.5. Estimates of the threshold doses for mortality* in adults exposed to acute, fractionated or protracted, and chronic irradiation.

Effect	Organ/tissue	Time to develop effect	Absorbed dose [†] resulting in approximately 1% incidence		
			Acute exposure (Gy)	Highly fractionated (2-Gy fractions) or equivalent protracted exposures (Gy) [‡]	Annual (chronic) dose rate for many years (Gy/year)
<i>Bone marrow syndrome</i>					
Without medical care	Bone marrow	30–60 days	~1	10	NA
With good medical care	Bone marrow	30–60 days	2–3	>10	NA
<i>Gastro-intestinal syndrome</i>					
Without medical care	Small intestine	6–9 days	~6	NA	NA
With conventional medical care	Small intestine	6–9 days	>6	40	NA
Pneumonitis – mean lung dose	Lung	1–7 months	7–8	15	NA
Cardiovascular disease – whole-body exposure	Heart	>10–15 years	~0.5	~0.5	~0.5 [§] divided by years duration
Cerebrovascular disease	Carotid artery	>10 years	~0.5	~0.5	~0.5 [§] divided by years duration

NA, not available.

* Some of these diseases may not be fatal, if good medical care or biological response modifiers are used (see Section 3). In the cases of cardiovascular disease and cerebrovascular disease, from the evidence currently available, the values given here are also assumed to apply to morbidity from these diseases.

[†] Most values rounded to nearest Gy; ranges indicate area dependence for skin and differing medical support for bone marrow.

[‡] Derived from fractionated radiotherapeutic exposures, generally using 2-Gy fractions. For other fraction sizes, the following formula can be used, where D is total dose (number of fractions multiplied by d), d is dose per fraction (2 Gy in the case of D_1 , and new value of d in the case of D_2), and the ratio α/β can be found in the appropriate section of this report: $D_1[1 + 2/(\alpha/\beta)] = D_2[1 + d_2/(\alpha/\beta)]$. Protracted doses at a low dose rate of around 1 cGy/min are approximately iso-effective to doses delivered in 2-Gy fractions at high dose rate for some tissues, but this equivalence is dependent on the repair half-time of the particular tissue. Further details can be found in Joiner and Bentzen (2009), Bentzen and Joiner (2009), and Van der Kogel (2009).

[§] The values quoted for the circulatory system assume the same incidence of injury irrespective of the acute or chronic nature of the exposure, with >15 years follow-up. It is emphasised that great uncertainty is attached to these values.

lens opacities. Epidemiological studies have variously used self-reporting, medically documented lens opacities, or cataract extraction surgery. Scoring systems for lens opacities have also varied. In addition, there remains much variability among clinicians and investigators in the precise clinical definition of a radiation cataract, and a diversity of opinion as to whether all detectable lens changes, given sufficient time, will progress to visually-disabling cataracts. A summary of results of many of the studies of radiation-induced lens changes (Section 2.6.1 and Annex A) is shown in Table 4.2 (see Tables 4.4 and 4.5).

(694) In view of the above problems with the early studies of radiation cataracts and reports in the past few years of markedly lower threshold doses deduced from various radiation exposure scenarios, it is prudent for ICRP to recommend changes to the threshold doses. The recent studies that have formally tested for an acute dose threshold (Table 4.3) for induction of opacities or cataracts show the following values with wide CIs:

- 0.50–0.70 Sv in the 2006 atomic bomb study for early PSC and cortical opacities (Nakashima et al., 2006).
- 0.10 Sv in the 2007 atomic bomb study for cataract surgery prevalence (Neriishi et al., 2007).
- 0.45–0.50 Sv for excess absolute risk and excess relative risk for incidence of cataract surgery (stronger than the prevalence study) in the 2010 atomic bomb study (Blakely et al., 2010; Shore et al., 2010).

Furthermore, infants treated with ^{226}Ra plaques for haemangioma and who received a mean dose of 0.40 Gy showed a dose–response relationship with an RR of 1.5 at 1 Gy for cortical and PSC opacities (Hall et al., 1999).

(695) For fractionated, protracted irradiation, an accumulated dose threshold of 0.35 Sv is indicated from the Chernobyl clean-up worker study for Stage 1 (early) PSC and cortical opacities (Worgul et al., 2007). An earlier study (Nadejina et al., 2002) reported ‘no radiation cataracts’ among recovery workers, but doses and assessment techniques were not stated.

(696) Regarding chronic irradiation, minor PSC opacities were reported in children in the Chernobyl area (doses unknown but probably much less than those described above), with an excess among those in the exposed areas compared with the unexposed area (Day et al., 1995). For interventional cardiologists, it was reported that the frequency and severity of PSC opacities increased with age and number of years of practice (5–36 years), but no dosage information was given (Junk et al., 2004). In a study of 35,700 US radiological technologists receiving highly fractionated cumulative doses of 0.005–0.060 Gy, it was reported that the incidence of cataracts was marginally higher in the 0.060-Gy dose group than in the 0.005-Gy group, and that three or more diagnostic x rays to the face/neck at baseline showed a significant elevation in subsequently reported cataracts (Chodick et al., 2008). In US astronauts, there were excess minor opacities after what were probably quite low but unknown doses, and it is unclear what proportion of dose would be from heavy ion exposures in space as opposed to the numerous x-ray screenings that the astronauts had undergone (Cucinotta et al., 2001; Chylack et al., 2009). An

excess of early and progressing opacities was found in young (<20 years) residents of ^{60}Co -contaminated buildings in Taiwan, exposed to low-dose-rate irradiation over several years, giving a wide range of individual doses with a mean cumulative dose of ~ 0.20 Sv (median dose of ~ 0.054 Sv) over ~ 7 years (Chen et al., 2001; Hsieh et al., 2010).

(697) Overall, the general consistency of the collective results for both early lens opacities and advanced cataracts makes a compelling 'weight of evidence' judgement that the recommended acute dose threshold for the purposes of radiation protection should be lowered from its current value to a nominal value of 0.50 Sv. This is subject to the caveats that the progressive nature of assessed opacities into cataracts, and the likely greater sensitivity of the lens in children compared with postadolescents, require further characterisation.

(698) For fractionated and protracted exposures, the current epidemiological evidence indicates that the threshold is not larger than that for acute exposures, although animal data suggest that a higher value might be plausible. For chronic exposure over several to many years, much of the evidence refers to opacities rather than frank cataracts. The uncertainties about progression of opacities into cataracts, and the age-at-exposure problem mentioned above, make difficult any judgement about dose thresholds for chronic exposures.

(699) In addition, it is suggested that there is a genetic component to the radiosensitivity of cataractogenesis, which may produce more cataracts in a few percent of exposed individuals. On the other hand, chemical agents that block lens cell proliferation might reduce cataract formation, although there are no established mitigating agents. Lastly, although the lower 95% CI in some threshold calculations includes zero dose, there is no direct evidence that a single damaged progenitor lens epithelial cell can produce a cataract, and hence radiation-induced lens cataract is still considered a tissue reaction (deterministic effect) with a dose threshold, albeit small.

4.8. Respiratory system

(700) The threshold values for pneumonitis are derived from whole-lung radiotherapeutic exposures, and the values of 6.5 Gy for acute exposures and 18 Gy for highly fractionated exposures are very similar to previous recommendations (apart from the slight reduction in thresholds for fractionated exposures, from 20 Gy to <18 Gy) (Section 2.7).

(701) There is clinical evidence that steroids can relieve the symptoms of pneumonitis, but it remains unclear whether they can protect against the development of late fibrosis. In a randomised clinical trial of breast or lung cancer patients, pentoxifylline given during the period of radiotherapy significantly reduced both early (3 month) and late (6 month) lung toxicity. A retrospective clinical analysis of lung cancer patients who received ACE inhibitors during radiotherapy (mostly for hypertension) concluded that this did not significantly reduce the risk of radiation pneumonitis.

4.9. Urinary tract

(702) In the urinary tract, the kidneys are the most sensitive organ, the bladder is more resistant, and the ureters are the most resistant tissue (Section 2.8). The threshold dose for renal failure is approximately 7 Gy acute dose, and 18 Gy for doses given as multiple 2-Gy fractions. Although extrapolations from multifraction to single dose effects using the LQ model are problematic, to a first approximation, these values are compatible with the value of the fractionation sensitivity parameter $\alpha/\beta = 2.5$ Gy deduced from studies using animal systems.

(703) For late reactions in the bladder, the threshold total fractionated (2-Gy fractions) dose is ≤ 50 Gy. If the value of α/β is 4 Gy, as deduced from some studies using animal systems, this threshold fractionated dose would extrapolate to a single dose of around 15 Gy. For the ureters, the threshold total fractionated dose is also suggested to be ≤ 50 Gy.

(704) The most promising agents to date in reducing BMT nephropathy are ACE inhibitors and AII receptor antagonists. Animal studies have shown DMFs of 1.2–1.5 when given prophylactically from the time of irradiation. Initial results from a series of 55 patients who received TBI/BMT showed a trend (non-significant) for increased survival and improved renal function in favour of the captopril-treated group. Anti-inflammatory agents have produced equivocal benefits in both human and animal systems, and drug dosage level appears to be an important factor.

4.10. Musculoskeletal system

(705) Radiation exposure can give rise to three different types of non-cancerous bone pathology: (a) osteoradionecrosis, (b) spontaneous fractures or fractures with less than normal trauma, or (c) abnormalities of bone growth. The threshold dose for necrosis of femoral heads and fractures of ribs is around 50 Gy in 2-Gy fractions. The acute single dose value is not known. In contrast to mature bone, growing bone is among the most radiosensitive of all tissues, and 25 Gy is often suggested as a critical threshold dose. For skeletal muscle, a tolerance dose of approximately 55 Gy (2-Gy fractions) has been estimated (Section 2.9).

(706) Hyperbaric oxygen therapy has been shown to have a positive effect in a number of delayed radiation injury situations, including musculoskeletal radiation injury, and this remains the only agent claimed to mitigate such clinical reactions at the present time. Other agents are being studied in preclinical systems.

4.11. Endocrine system

(707) Brain irradiation can have direct radiation effects on the thyroid and pituitary glands, as well as subtle effects on the hypothalamic–pituitary–adrenal axis and the hypothalamic–pituitary–gonadal axis (Section 2.10). All of the information comes from radiotherapy experience using fractionated doses, generally of 2 Gy per fraction. The hypothalamus is more radiosensitive than the pituitary. In children, radiation effects include GH deficiency, precocious puberty (after lower doses) or

delayed puberty (after higher doses), hypopituitarism, and hyperparathyroidism. In adults, radiation effects include hyperprolactinaemia, hypogonadism, obesity, hypothyroidism, hyperthyroidism, and ACTH deficiency.

(708) There are various strategies for mitigating the effects of radiation on the endocrine system. These include GH replacement in children with radiation-induced GH deficiency, thyroid hormone replacement therapy in cases of its deficiency, and repeated intermittent infusion of GnRH in cases of reduced gonadotropin secretion after pituitary damage. However, there is insufficient evidence of the efficacy of these procedures to calculate a radiation DMF.

4.12. Nervous system

(709) The threshold dose for symptomatic spinal cord injury (myelitis) is approximately 50 Gy delivered in 2-Gy fractions. The injury is highly dependent on dose per fraction, and the threshold dose is greater when very small volumes (<1 cm cord length) are irradiated. The threshold dose for acute single doses in humans is not known. The adult brain has been considered rather more resistant in terms of necrosis, but subtle effects have been detected at much lower doses of around 10 Gy, and clear volume effects are discernable. Low-dose irradiation (1–2 Gy) to the developing brain of children can cause long-term cognitive and behavioural defects, and infants are even more susceptible with cognitive impairment in adult life detected after exposure to doses of >0.1 Gy before 18 months (Section 2.11).

(710) There are no recognised mitigating agents for use in humans to treat spinal cord injury after irradiation. Preclinical studies with anti-inflammatory agents, ACE inhibitors and AII receptor antagonists, some growth factors, and PUFAs have shown the most promise. Clinical trials using bevacizumab, a monoclonal antibody against VEGF, after brain irradiation have reported significant reductions in brain oedema, albeit in small numbers of patients. Also, there are anecdotal reports of the benefits of steroids and anticoagulant therapies after brain irradiation.

4.13. Conclusions

(711) This report has produced some changes to indicated threshold doses for tissue reactions (see Tables 4.4 and 4.5) compared with those stated in *Publication 103* (ICRP, 2007). First, the threshold dose for radiation-induced eye cataracts is now considered to be around 0.5 Gy for both acute and fractionated/chronic exposures, in line with various recent epidemiological studies. Second, circulatory disease has been recognised as an important late effect of radiation exposure, both for mortality and morbidity. An approximate threshold dose of around 0.5 Gy has been proposed for acute and fractionated/protracted exposures, on the basis that this might lead to circulatory disease in only one to a few percent of exposed individuals, although the estimation of risk at this level of dose is particularly uncertain.

(712) Third, the threshold dose values for chronic exposures depend on the exposure duration and the follow-up period after exposure. Differences between these time variables among different studies make the values more uncertain. The values quoted for both the lens and the circulatory system assume the same incidence of injury irrespective of the acute or chronic nature of the exposure over a working life, with >20 years follow-up. Future studies may elucidate this further. For the public, the annual threshold dose values would be scaled down in proportion to relative life span minus latency period (20 years latency for lens, 10 years for circulatory disease) vs working life. It is emphasised that great uncertainty is attached to these values.

(713) Fourth, much more information has become available regarding the effect of biological response modifiers in mitigating the tissue reactions, which has the effect of modifying threshold doses. These modifications are agent, tissue, and schedule specific, and they are likely to have increasing impact in the future, concomitant with increases in scientific and medical knowledge.

(714) As a general conclusion, ICRP judges, on the basis of existing evidence, that acute doses up to around 0.10 Gy produce no functional impairment of tissues. This includes the lens of the eye regarding the risk of cataract, with the caveat that the use of a threshold model remains uncertain for this tissue. Hence for most applications of ICRP recommendations in occupational or public situations, the stochastic risks of induced cancer and hereditary effects remain the principal risks to consider. At higher doses, the risk of tissue reactions (deterministic effects) becomes increasingly important, particularly regarding radiation incidents and accidents, and medical exposures.

4.14. References

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ANNEX A. SUMMARY OF STUDIES OF EXPOSURE AND OPACITIES OR CATARACTS

(A1) This summary was compiled by Dr. Roy E. Shore, Japan, and primarily relates to low-LET radiation. Articles are in chronological order, except for the chronological series of Japanese atomic bomb studies which are listed together at the end.

Author and date	Cogan and Dreisler (1953)
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Reference	Cogan, D.G., Dreisler, K.K., 1953. Minimal amount of X-ray exposure causing lens opacities in the human eye. <i>AMA Arch. Ophthalmol.</i> 50, 30–34
Type of study	Case reports from clinical records
Number of individuals	40 cases with history of x ray near eyes
Ages at exposure	15–70 years
Gender distribution	70% females
Participation rate	N/A
Dose	23–2400 rad (estimates based on phantom reconstructions)
Radiation type	100–200 kV x ray (except one case of 1200 kV)
Dose rate	Single exposure up to 5 months fractionated
Technique for assessment	Ophthalmoscopy or slit-lamp
Endpoint (subgroups?)	‘Lens changes... characteristic of irradiation’
Ages at observation	17–71 years (53% <30 years)
Follow-up time	1.3–14 years (mean 7.3 years overall and 8.0 years for those without cataracts)
Confounders evaluated?	None
Description of results	Five radiation cataracts noted, none of which were among the 33 persons with <500 rad
Threshold dose (CI)	–
Prevalence at 1 Gy (95% CI)	–
Comments	Small irradiated case series with a short follow-up time

Author and date	Merriam and Focht (1957)
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Reference	Merriam, G.R., Focht, E.F., 1957. A clinical study of radiation cataracts and the relationship to dose. <i>Am. J. Roentgenol. Rad. Ther. Nucl. Med.</i> 77, 759–784 (Also: Merriam, G.R., Szechter, A., Focht, E., 1972. The effects of ionizing radiations on the eye. <i>Front. Radiat. Ther. Oncol.</i> 6, 346–385)
Type of study	Case series from clinical records
Number of individuals	Searched clinical records for 100 persons with radiation opacities/cataracts and found 73 with head irradiation (x ray or radium) and no lens opacities
Ages at exposure	1 month–84 years
Gender distribution	49% females
Participation rate	N/A
Dose	Based on retrospective dose reconstruction with a phantom, range 25–6900 rad In cataract group: 0%, <200 rad; 4%, 200–350 rad; 26%, 400–1000 rad; 19%, 1000–2000 rad; 11%, 2000–4000 rad; 11%, >4000 rad; 29%, dose unknown (but nearly all >1500 rad) In non-cataract group: 33 (45%), <200 rad; 11 (15%), 200–399 rad; 27 (37%), 400–999 rad; 2 (3%), >1000 rad
Radiation type	100–140 kV or 200–250 kV x ray, or radium plaque/seed

Dose rate	37 with single x ray or radium plaque, 87 with multiple radiotherapy over 3 weeks–3 months, 49 over >3 months
Technique for assessment	Either ophthalmoscope or slit-lamp (proportions unknown)
Endpoint (subgroups?)	‘Any clinically recognizable opacity having the characteristic appearance [of a radiation cataract], irrespective of whether or not vision was affected’; categorised them as ‘stationary’ or ‘progressive’ cataracts
Ages at observation	2–>85 years
Follow-up time	Diagnosis of cataract, mean 4.8 years after first radiotherapy. Those without cataract and with estimated lens dose of <200 rad, last eye examination mean 9.3 years after radiotherapy
Confounders evaluated?	Examined age-at-exposure effect, informally considered complicating factors (haemorrhage, glaucoma, uveitis)
Description of results	All cataract cases had estimated doses of ≥ 200 rad. For cataracts after divided exposures of >3 months, the minimum dose was >500 rad. Reported an inverse relationship between lens dose and time to cataract, and greater sensitivity among those young at exposure (findings based on crude tabulations and no statistical testing)
Threshold dose (CI)	Indicated 200 rad for any opacity, approximately 500 rad for ‘progressive’ cataracts
Prevalence at 1 Gy (95% CI)	0
Comments	Based on a clinical case series, not on a defined cohort. The number of persons with lens doses of <200 rad was grossly inadequate (only 33) and the follow-up times after irradiation were short (mean 9.3 years) Although this became the major basis for radiation standards for several decades, the study would be regarded as substantially inadequate by modern-day epidemiological standards

Author and date	Qvist and Zachau-Christiansen (1959)
Reference	Qvist, C.F., Zachau-Christiansen, B., 1959. Radiation cataract following fractionated radium therapy in childhood. <i>Acta Radiol.</i> 51, 207–216
Type of study	Sample of a cohort who had received radium therapy for haemangiomas
Number of individuals	855 patients with treatment to the head; 112 patients who were estimated to have received a lens dose of >100 rad were selected, and 56 were examined
Ages at exposure	Infancy
Gender distribution	Unknown
Participation rate	51%
Dose	Estimated lens doses by calculations
Radiation type	Gamma from radium applicators
Dose rate	1–15 treatments (over ≥ 10 months)
Technique for assessment	Ophthalmological examination (methods unspecified)
Endpoint	Cataract
Ages at observation	Not specified (>20–>40 years)
Follow-up time	Not specified (>20–>40 years)
Confounders evaluated?	None noted
Description of results	‘4 cases of unmistakable radiation cataract’, all with doses of ≥ 690 rad. However, in addition, one opacity was found with an estimated dose of 10–35 rad, which they did not consider to be a ‘radiation cataract’, one ‘senile cataract’ at 40 years of age with a dose of 640 rad, and one ‘congenital cataract’ with a dose of 25 rad

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Threshold dose (CI)	690 rad
Prevalence at 1 Gy (95% CI)	0 (but see the note above about a low-dose cataract)
Comments	Small study with unspecified methods of ophthalmological examination. They specifically targeted those thought to have received >100 rad

Author and date	Albert et al. (1968)
Reference	Albert, R., Omran, A., Brauer, E., et al., 1968. Follow-up study of patients treated by X-ray epilation for <i>Tinea capitis</i> . II. Results of clinical and laboratory examinations. Arch. Environ. Health 17, 919–934
Type of study	Screening of subsample of irradiated cohort
Number of individuals	234 exposed, 232 unexposed
Ages at exposure	1–14 years, mean 7.7 years
Gender distribution	10% females
Participation rate	~50%
Dose	Eye dose ~0.50 Gy
Radiation type	X ray
Dose rate	Five unequal fractions a few minutes apart
Technique for assessment	Slit-lamp examination, examiner blinded to radiation status
Endpoint	Abnormal luminescence and early PSC opacities
Ages at observation	Median 17 years (68% aged 10–19 years, 32% aged ≥20 years)
Follow-up time	~10 years
Confounders evaluated?	Sex, race (37% Blacks, 63% Whites), age
Description of results	Exposed vs non-exposed: no difference for abnormal luminescence or non-PSC opacities. PSC opacities: 13 irradiated and two control cases (age-adjusted OR 5.9, 95% CI 1.4–24). PSC opacities were ‘very mild’
Threshold dose (CI)	–
Prevalence at 1 Gy (95% CI)	–
Comments	Small study of opacities at young ages after ~0.5-Gy x-ray dose to eye

Author and date	Day et al. (1995)
Reference	Day, R., Gorin, M.B., Eller, A.W., 1995. Prevalence of lens changes in Ukrainian children residing around Chernobyl. Health Phys. 68, 632–642
Type of study	Cross-sectional prevalence study
Number of evaluable individuals	991 from two towns/areas with high depositions, 791 from a town with virtually no deposition
Ages at exposure	0–12 years
Gender distribution	53% female in both groups
Participation rate	35–40%, but participation due to factors other than self-selection
Dose	Area deposition of ¹³⁷ Cs: 55–148 × 10 ¹⁰ Bq/km ² estimates of cumulative dose 1986–1989 range from 29 to 35 mSv (or 86 mSv by cytogenetic methods)
Radiation type	See above
Dose rate	See above
Technique for assessment	Slit-lamp, LOCS III + ‘focal lens defects’ (i.e. vacuoles, flakes, dots)
Endpoint (subgroups?)	LOCS III ≥2
Ages at observation	49% aged 5–11 years, 51% aged 12–17 years
Follow-up time	5.7 years
Confounders evaluated?	Diabetes, radiotherapy, daily medications

Description of results	No difference in cortical opacities ≥ 2 [exposed 15 (1.5%), unexposed 10 (1.3%)]. PSC opacities ≥ 2 [exposed 5 (0.5%), unexposed 0, $P = 0.05$]. Total PSC opacities (≥ 1) [exposed 28 (2.8%), unexposed 8 (1.0%), $P = 0.005$]
Threshold dose (CI)	–
Prevalence at 1 Gy (95% CI)	–
Comments	Ophthalmologists knew of the subjects' exposure status. However, they had standardisation, retraining and reliability evaluation, examination of positive lenses by two examiners, plus slit-lamp photographs of positive lenses

Author and date	Wilde and Sjostrand (1997)
Reference	Wilde, G., Sjostrand, J., 1997. A clinical study of radiation cataract formation in adult life following γ irradiation of the lens in early childhood. <i>Br. J. Ophthalmol.</i> 81, 261–266
Type of study	Opacity prevalence in a small cohort treated with ^{226}Ra for haemangioma of the eyelid
Number of individuals	20
Ages at exposure	2–13 months
Gender distribution	Unknown
Participation rate	100%
Dose	1–11 Gy to treated side, 0.02–0.12 Gy to untreated side
Radiation type	Gamma
Dose rate	Given over 1.5–3 h
Technique for assessment	Slit-lamp biomicroscopy and retro-illumination photography
Endpoint (subgroups?)	'Radiation cataract'
Ages at observation	31–46 years
Follow-up time	30–46 years
Confounders evaluated?	None noted
Description of results	No formal statistics. All treated eyes had opacities. Opacity grade increased with lens dose. 13 of 20 contralateral lenses had very minor opacities
Threshold dose (CI)	–
Prevalence at 1 Gy (95% CI)	–
Comments	Carefully conducted, but small study contributes little quantitative information

Author and date	Hall et al. (1999)
Reference	Hall, P., Granath, F., Lundell, M., Olsson, K., Holm, L.-E., 1999. Lenticular opacities in individuals exposed to ionizing radiation in infancy. <i>Radiat. Res.</i> 152, 190–195
Type of study	Cohort study, screening prevalence
Number of individuals	484 exposed, 89 non-exposed
Ages at exposure	Mean 5 months, range 0–16 months
Gender distribution	Exposed 72% females, non-exposed 74%
Participation rate	80%
Dose	Mean 0.4 Gy, range 0–8.4 Gy
Radiation type	88% from ^{226}Ra , rest from contact x ray (≤ 60 kVp)
Dose rate	Mean of 2.1 treatments, range 1–14. ^{226}Ra dose rate to lenses: mean 0.13 Gy/h, median 0.05 Gy/h, maximum 3.0 Gy/h
Technique for assessment	LOCS system, score ≥ 1 considered positive
Endpoint (subgroups?)	Cortical and PSC opacities

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Ages at observation	46 years (range 36–54 years)
Follow-up time	46 years
Confounders evaluated?	Diabetes, steroid treatment, family history of cataract, other eye disorder, other radiotherapy
Description of results	Cortical + PSC cataract prevalence by dose (mGy): 0 = 9/178 (5%), 1–499 = 89/747 (12%), 500–999 = 20/115 (18%), $\geq 1000 = 20/89$ (22%)
Threshold dose (CI)	–
Prevalence at 1 Gy (95% CI)	Cortical: 1.50 (95% CI 1.15–1.95); PSC: 1.49 (95% CI 1.07–2.08)
Comments	Nuclear cataracts were not related to radiation dose. Dose–response analysis was limited to exposed group because non-exposed group was insufficiently comparable

Author and date	Nadejina et al. (2002)
Reference	Nadejina, N.J., Galstian, I.A., Savitsky, A.A., et al., 2002. Chronic irradiation: tolerance and failure in complex biological systems. <i>Br. J. Radiol. Suppl.</i> 26, Fliedner, T., Feinendegan, L.E., Hopewell, J.W. (Eds.), 50–54.
Type of study	Cohorts of 13 people with ARS and 30 recovery operation workers
Number of individuals	11 people with ARS and 30 recovery workers
Ages at exposure	Mean ~35 years for people with ARS, ~37 years for recovery workers
Gender distribution	<10% females
Participation rate	Complete
Dose	People with ARS: minimum dose 2.6 Gy, average estimated as ~3.2 Gy. Recovery workers: estimated mean dose 0.2 Gy
Radiation type	Gamma and beta
Dose rate	People with ARS: high dose rate. Recovery workers: protracted
Technique for assessment	Repeated ophthalmologic examinations over 14 years (instrumentation not specified)
Endpoint	Cataracts
Ages at observation	Up to 14 years older than exposures
Follow-up time	Approximately 14 years
Confounders evaluated?	None
Description of results	Five of 11 ARS cases had radiation cataracts. No radiation cataracts but three senile cataracts in the recovery workers
Threshold dose (CI)	–
Prevalence at 1 Gy (95% CI)	–
Comments	They mention a Russian language publication that reported 13 cataract cases in ARS subjects

Author and date	Junk et al. (2004)
Reference	Junk, A.K., Haskal, Z., Worgul, B.V., 2004. Cataract in interventional radiology – an occupational hazard? <i>Invest. Ophthalmol. Vis. Sci.</i> 45, E-abstract 388
Type of study	Cross-sectional screening study of 59 interventional radiologists
Number of individuals	59
Ages at exposure	Not reported
Gender distribution	Not reported
Participation rate	Unknown
Dose	Unknown
Radiation type	X ray

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Dose rate	Occupationally exposed from 5 to 36 years
Technique for assessment	Scheimpflug examination after pupil dilation
Endpoint	Precataract changes and PSC cataracts
Ages at observation	29–62 years
Follow-up time	No follow-up but had been exposed 5–36 years previously
Confounders evaluated?	Age, handedness
Description of results	22 showed 'small paracentral dot-like opacities' in PSC region, and PSC cataracts found in nine eyes of five persons. Concluded that the frequency and severity of PSC opacities increased with age and number of years in the field
Threshold dose (CI)	–
Prevalence at 1 Gy (95% CI)	–
Comments	Suggestion that chronic radiation exposure may lead to opacity formation. No dose estimates

Author and date	Shang and Fu (2007)
Reference	Shang, B., Fu, E., 2007. Investigation on incidence of lens opacity in radiation workers. <i>Chin. J. Indust. Med.</i> 20, 48–49 (in Chinese; information below from an ICRP C1 summary provided by Dr. Pingkun Zhou)
Type of study	Cross-sectional screening of workers
Number of individuals	584 occupational radiation workers plus 340 controls
Ages at exposure	Not specified in the summary available
Gender distribution	Not specified in the summary available
Participation rate	Unknown
Dose	Only years of radiation work given: 4 months–35 years (mean 11.6 years)
Radiation type	Not specified in the summary available
Dose rate	Protracted, likely low dose rate
Technique for assessment	Slit-lamp
Endpoint	Opacities and early changes
Ages at observation	20–57 years
Follow-up time	4 months–35 years
Confounders evaluated?	Not specified in the summary available. No indication that adjustment was made for age
Description of results	Found increase in more advanced (but still early) opacities with longer radiation working time
Threshold dose (CI)	–
Prevalence at 1 Gy (95% CI)	–
Comments	The study does not provide sufficient quantitative information, but suggests some concern regarding radiation workers with past levels of radiation exposure

Author and date	Worgul et al. (2007)
Reference	Worgul, B.V., Kundiyeve, Y.I., Sergiyenko, N.M., et al., 2007. Cataracts among Chernobyl clean-up workers: implications regarding permissible eye exposures. <i>Radiat. Res.</i> 167, 233–243 (See also: Chumak, V.V., Worgul, B.V., Kundiyeve, Y.I., et al., 2007. Dosimetry for a study of low-dose radiation cataracts among Chernobyl clean-up workers. <i>Radiat. Res.</i> 167, 606–614)

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Type of study	Two ophthalmological screenings of an occupationally exposed cohort of Chernobyl clean-up workers
Number of individuals	8607 screened twice
Ages at exposure	8.5%, <25 years; 14%, 25–29 years; 23%, 30–34 years; 34%, 35–39 years; 53%, ≥40 years
Gender distribution	4% females
Participation rate	11,797 lived in relevant oblast and had address information, 73% of those were examined
Dose	0–>1 Gy (2% received >0.7 Gy)
Radiation type	Gamma and beta
Dose rate	Exposures over 1 to several months
Technique for assessment	Ophthalmoscopic and slit-lamp assessment. Ophthalmologists were trained for standardised assessment, but opacity rates varied by examiner
Endpoint	Opacities: nuclear, non-nuclear, cortical, PSC, graded by the Merriam–Focht scoring system
Ages at observation	26%, <40 years; 50%, 40–49 years; 14%, 50–54 years; 10%, ≥55 years
Follow-up time	Examinations at 12 and 14 years after clean-up work commenced (1986–1987)
Confounders evaluated?	Smoking, age, sex, diabetes, corticosteroids, occupations with exposure to chemicals, radiation, UV radiation, infrared, examiner scoring variations
Description of results	1817 (21%) had Stage 1 posterior cortical opacity in one/both eyes, 1464 (17%) had Stage 1 PSC opacity, 90 (1.1%) had Stage 2–5 non-nuclear opacity
Threshold dose (CI)	Stage 1 posterior cortical opacity, 0.34 Gy (95% CI 0.18–0.51); Stage 1 PSC opacity, 0.35 Gy (95% CI 0.19–0.66)
Odds ratio at 1 Gy (95% CI)	Stage 1–5 non-nuclear opacity, 1.65 (95% CI 1.18–1.65); Stage 1 posterior cortical opacity, 1.51 (95% CI 1.09–2.10); Stage 1 PSC opacity, 1.42 (95% CI 1.01–2.00)
Comments	Adjustment was made for variations between examiners, but no photographs of lenses were taken. Nearly all opacities were mild and did not affect vision, but ages were still young. Individual doses were mainly estimated from ‘official doses’ with adjustments based on a limited comparative set of Electron Paramagnetic Resonance dose estimates, and not actual dosimeter readings, so individual dose uncertainties were substantial.

Author and date	Chodick et al. (2008)
Reference	Chodick, G., Bekiroglu, N., Hauptmann, M., et al., 2008. Risk of cataract after exposure to low doses of radiation: a 20-year prospective cohort study among US radiologic technologists. <i>Am. J. Epidemiol.</i> 168, 620–631
Type of study	Mail questionnaire self-reports of cataracts among radiological technologist cohort
Number of individuals	35,705 workers with usable data
Ages at exposure	14–43 years before study entry
Gender distribution	83% females
Participation rate	54% of those eligible
Dose	Considered number of x rays to the face/neck, and estimated cumulative occupational radiation exposure
Radiation type	Primarily x-ray exposure
Dose rate	Highly fractionated, over <6–>13 years
Technique for assessment	Mail surveys of cataracts and numerous potential risk factors
Endpoint	Reported cataract and reported cataract surgery

Ages at observation	~43–64 years
Follow-up time	19.2 ± 1.8 years
Confounders evaluated?	>20 variables, including sociodemographic, lifestyle and medical/medication history, and UV exposure index
Description of results	2382 cataracts reported (591 before 50 years of age) and 647 cataract extractions (183 before 50 years of age). Found that those who reported ≥3 diagnostic x rays to the face/neck on the baseline questionnaire subsequently had greater cataract incidence: HR = 1.25 (95% CI 1.06–1.47, $P < 0.01$). Radiotherapy to the head before 15 years of age: HR = 1.41 (95% CI 1.00–1.99) (after 15 years of age was 1.27, not statistically significant) Total number of diagnostic x rays (to any part of body) was associated with cataract extraction: HR = 1.50 (95% CI 1.09–2.06). Radiotherapy to head/neck, HR = 1.71 (95% CI 1.09–2.68) Occupational radiation exposure: dose–response, ERR/Gy = 1.98 (95% CI –0.69 to 4.65, $P = 0.15$). Those in highest vs lowest dose categories (means of 60 vs 5 mGy), HR = 1.18 (95% CI 0.99–1.40, $P = 0.06$). For cataract surgery, ERR/Gy = 1.50 (95% CI –3.43 to 6.43)
Threshold dose (CI)	Found marginally significant difference between workers in highest (mean = 60 mGy) and lowest (mean = 5 mGy) dose categories
Relative risk at 1 Gy (95% CI)	For total reported cataracts, HR/Gy = 1.98 (95% CI –0.69 to 4.65). For cataract extractions, HR/Gy = 1.50 (95% CI –3.43 to 6.43)
Comments	A large study. Based on self-reported cataracts and cataract surgeries. Probably appreciable dose uncertainties, especially for those employed before approximately 1955 when there was limited film-badge information

Author and date	Kleiman et al. (2009)
Reference	Kleiman, N.J., Cabrera, M., Duran, G., Ramirez, R., Duran, A., Vañó, E., 2009. Occupational risk of radiation cataract in interventional cardiology. Invest. Ophthalmol. Vis. Sci. Presentation abstract 511/D656
Type of study	Cross-sectional screening study
Number of individuals	78 medical IC personnel
Ages at exposure	Adult
Gender distribution	Not stated
Participation rate	Volunteers, participation rate unknown
Dose	Unknown
Radiation type	X ray
Dose rate	Protracted
Technique for assessment	Slit-lamp examination after pupil dilation, scored by three independent observers
Endpoint	PSC lens changes and opacities
Ages at observation	22–69 years for IC doctors (mean 46.7 years), 20–58 years for other personnel (mean 32.2 years)
Follow-up time	1–40 years of IC experience
Confounders evaluated?	Obtained medical history but not used in analysis
Description of results	18/42 IC doctors had PSC changes consistent with radiation exposure (10/18 had bilateral changes, 12/18 seldom/never used eye protection, 13/18 did not use leaded ceiling screens). 3/34 IC nurses or technicians had mild PSC changes
Threshold dose (CI)	–
Prevalence at 1 Gy (95% CI)	–

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Comments Doses not known. Doctors were older than nurses/technicians. Study suggests that protracted radiation exposures may lead to opacities, but age needs to be ruled out

Author and date Hsieh et al. (2010)

Reference Hsieh, W.A., Lin, I.-F., Chang, W.P., Chen, W.-L., Hsu, Y.H., Chen, M.-S., 2010. Lens opacities in young individuals long after exposure to protracted low-dose-rate gamma radiation in ⁶⁰Co-contaminated buildings in Taiwan. *Radiat. Res.* 173, 197–204

Chen, W., Hwang, J., Hu, T., Chen, M.S., Chang, W.P., 2001. Lenticular opacities in populations exposed to chronic low-dose-rate gamma radiation from radiocontaminated buildings in Taiwan. *Radiat. Res.* 156, 71–77

Type of study Examination of opacity prevalence in cohort of those exposed to chronic gamma radiation in ⁶⁰Co-contaminated residences

Number of individuals 73 persons under 20 years of age when first examined in 1998. Also examined 4.7 years later. Comparison group of 100 healthy volunteers without exposure (ages 6–22 years)

Ages at exposure Exposed for up to 15 years

Gender distribution 44% females

Participation rate 87% included. Exclusions due to not providing information or having other health conditions

Dose Cumulative estimated doses: ~190 ± 357 mSv (mean), ~54 mSv (median)

Radiation type Chronic gamma irradiation (up to 15 years)

Dose rate Mean 7.4 ± 3.7 years of exposure

Technique for assessment Slit-lamp examination after pupil dilation

Endpoints LOCS-III assessment, plus FLD to grade minor opacities

Ages at observation 14.9 ± 3.8 years

Follow-up time Exposures ceased from <1 to >5 years before the examination

Confounders evaluated? Age, time since exposure ceased

Description of results Found increase in FLD between the first and second examinations, and a significant (*P* = 0.002) increase in FLD in the exposed group. The exposure-associated increase in FLD was found in the anterior cortex, but not the posterior cortex or nucleus

Threshold dose (CI) –

Prevalence at 1 Gy (95% CI) –

Comments Study suggests an increase in minor opacities or pre-opacities at around 0.2 Gy of chronic radiation exposure

Japanese atomic bomb studies

Author and date Cogan et al. (1949)

Cogan et al. (1950)

Reference Cogan, D.G., Martin, S., Kimura, S., 1949. Atomic bomb cataracts. *Science* 110, 654–655

Cogan, D.G., Martin, S.F., Kimura, S., Ikui, H., 1950. Ophthalmologic survey of atomic bomb survivors in Japan, 1949. *Trans. Am. Ophthalmol. Soc.* 48, 63–87

Type of study Screening in 1949 (4 years after atomic bomb exposure)

Number of individuals 1000 persons within 2000 m of hypocentre, randomly drawn from census files, of whom 231 were within 1000 m

Ages at exposure	See ages at observation
Gender distribution	Unknown
Participation rate	Not stated, but apparently high
Dose	Unknown, but included high (<1000 m) and low–intermediate (>1000 m) doses
Radiation type	Gamma + neutron
Dose rate	Instantaneous
Technique for assessment	Examination with ophthalmoscope and slit-lamp (but not all had slit-lamp; proportion unknown)
Endpoint (subgroups?)	Opacities characteristic of radiation (which apparently meant axial opacities)
Ages at observation	Most were 16–20 years of age (18%) or 6–10 years of age (12%) in 1949. Very few aged >60 years
Follow-up time	4 years
Confounders evaluated?	Other ocular findings noted
Description of results	No cases of ‘radiation cataract’ in the 769 individuals within 1000–2000 m of the hypocentre. 81 lens abnormalities noted in the 231 individuals within 1000 m, but none considered to be ‘unquestionable cases of radiation cataract’
Threshold dose (CI)	–
Prevalence at 1 Gy (95% CI)	–
Comments	Screening study 4 years after atomic bomb exposure. Their definition of ‘radiation cataract’ may have excluded an unknown number of cases (e.g. 38 had cortical cataracts, some of which may have been radiation-related)

Author and date	(N) Nefzger et al. (1969) (O82) Otake and Schull (1982) (O90) Otake and Schull (1990) (O96) Otake et al. (1996)
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References	(N) Nefzger, M.D., Miller, R.J., Fujino, T., 1969. Eye findings in atomic bomb survivors of Hiroshima and Nagasaki: 1963–1964. <i>Am. J. Epidemiol.</i> 89, 129–138 (O82) Otake, M., Schull, W., 1982. The relationship of gamma and neutron radiation to posterior lenticular opacities among atomic bomb survivors in Hiroshima and Nagasaki. <i>Radiat. Res.</i> 92, 574–595 (O90) Otake, M., Schull, W., 1990. Radiation-related posterior lenticular opacities in Hiroshima and Nagasaki atomic bomb survivors based on the DS86 dosimetry system. <i>Radiat. Res.</i> 121, 3–13 (O96) Otake, M., Neriishi, K., Schull, W.J., 1996. Cataract in atomic bomb survivors based on a threshold model and the occurrence of severe epilation. <i>Radiat. Res.</i> 146, 339–348
Type of study	Screening of a stratified random sample of atomic bomb survivors
Number of individuals	(N) 2468: 1627 in Hiroshima, 841 in Nagasaki, examined in 1963–1964 (O82) 2125: 1394 in Hiroshima, 731 in Nagasaki (O90) 1983 with DS86 doses: 1325 in Hiroshima, 658 in Nagasaki (O96) 1742 with DS86 doses and information on epilation
Ages at exposure	All ages, plus in utero. (O90) In utero not included as only one case of opacity
Gender distribution	Not reported in either (N) or (O82)
Participation rate	~70%

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Dose	<p>Dose groups: (N) 'high' = estimated dose of ≥ 200 rad (T57 doses) or ≥ 100 rad if in utero ($n = 1026$), 'low' = within 2000 m but < 200 (or 100) rad ($n = 789$); 'minimal' = 3000–9999 m ($n = 388$). Not in city ($n = 265$)</p> <p>(O82) Not in city = 263, 0 rad = 264, 1–99 rad = 627, 100–199 rad = 417, 200–399 rad = 368, 400–599 rad = 120, ≥ 600 rad = 65, unknown = 1. Group doses by 100-m distance only, estimated from preliminary DS86 using 'free in air' doses times shielding factors of 0.9 in Hiroshima, 0.85 in Nagasaki. Shielding factors are now believed to be more like 0.4–0.7, so mean doses were likely overestimated</p> <p>(O90) 71 of the 76 had DS86 doses</p> <p>(O90 and O96) Used individual DS86 doses</p>
Radiation type	Gamma + neutron
Dose rate	Instantaneous
Technique for assessment	Ophthalmoscope (+ slit-lamp if ophthal. positive). Examiners blinded to dose but indicated that exposure information may have been communicated in interactions by examinees
Endpoints	<p>(N) Axial opacities, cortical opacities, nuclear opacities, polychromatic changes. Only 84 axial opacities were considered 'radiation opacities'. Approximately 70% were classified as 'equivocal, minimal (< 1 mm), or small (1–2.4 mm). The rest were 'moderate' (~24%) or 'large' (five cases)</p> <p>(O90) 71 cases used after review of records rejected, some as not being PSC opacities and some with unknown dose</p>
Ages at observation	17–>50 years (not otherwise specified)
Follow-up time	18–19 years
Confounders evaluated?	<p>(N) Not stated, other than age</p> <p>(O82) In Hiroshima, those > 100 rad were 3–4 years younger than those < 100 rad</p> <p>(O90) Reported higher dose groups were of significantly older age</p> <p>The participation rate was somewhat higher in the exposed groups than in the 'not in city' or 0 dose groups. Questionnaire data indicated that participants were more concerned about their vision than non-participants</p>
Description of results	<p>(N) 84 axial opacities – increased in high-dose group. No dose-related differences in cortical or nuclear opacities. Gradient in posterior polychromatic changes seen by dose for both postnatal and prenatal exposure</p> <p>(O82) Based on re-review, accepted 76 axial opacities</p>
Threshold dose (CI)	<p>(N) Increased axial opacities only seen in high-dose group. They indicated that 'new' T65 doses were two to three times lower for Hiroshima than their T57 dose estimates, but little change was seen for Nagasaki dose estimates</p> <p>(O82) Best-fit was a linear-gamma and linear-neutron model with a likely T65 dose threshold of approximately 1.1 Gy (95% CI 0.6–1.5) for gamma (depending on which dosimetry estimates used), but no independent dose effect for neutron (due to the high gamma-neutron correlation)</p> <p>(O90) Best fit was a linear-gamma and linear-neutron model, both with dose thresholds. For eye doses, the best estimate of thresholds was 0.73 Gy (upper 95% CI 1.39) for gamma and 0.06 Gy for neutron. For gamma + neutron combined, the threshold was 1.46 Sv (but if a 35% dose error correction were applied, then the likely threshold would be between 1.54 and 1.68 Sv)</p> <p>(O96) Once 35% individual dose uncertainty was factored in and using gamma + $10\times$ neutron eye doses, the threshold estimates were 1.21 Sv for the epilation group and 1.41 Sv for the no-epilation group</p>
Prevalence at 1 Gy (95% CI)	–

Comments (N) First cataract study of atomic bomb survivors with reasonably good epidemiological methods. Limited, and probably inaccurate, dosimetry. No individual dosimetry (N and O82), but used DS86 doses for (O90 and O96) (N) Unable to estimate separate gamma and neutron effects, whereas O82 and O90 did so. Opacity ascertainment was limited because slit-lamp was used primarily when ophthalmoscopy was positive (O90) Gamma and neutron are highly correlated, so attempting to estimate separate gamma and neutron effects is questionable, especially since it was only based on 71 opacity cases. Therefore, the combined gamma–neutron dose threshold of approximately 1.4 Sv is probably more meaningful

Author and date	Choshi et al. (1983)
Reference	Choshi, K., Takaku, I., Mishima, H., et al., 1983. Ophthalmologic changes related to radiation exposure and age in Adult Health Study sample, Hiroshima and Nagasaki. <i>Radiat. Res.</i> 96, 560–579*
Type of study	Screening study of atomic bomb cohort. Attempted to screen all with ≥ 100 rad and an age- and sex-matched sample with 0 dose, plus all those scored as having axial opacities or PSC changes by previous Nefzger (1969) study
Number of individuals	No. examined: prenatal ATB: at the time of the bombing 84; postnatal ATB 2301
Ages at exposure	Examinations 33–35 years after exposure. Ages from prenatal to ≥ 50 years
Gender distribution	62% females
Participation rate	Postnatal ATB, 47% of eligible; prenatal ATB, 29%. Participation rate did not differ by dose
Dose	Used T65DR dosimetry system
Radiation type	Gamma + neutron
Dose rate	Instantaneous
Technique for assessment	Ophthalmoscopy + slit-lamp (but pupil dilation was seldom used). Lens lesions were photographed. Examiners blinded to dose group
Endpoint	Primarily axial opacities. Also examined PSC early changes
Ages at observation	181 (8%), <40 years; 521 (24%), 40–49 years; 739 (34%), 50–59 years; 385 (18%), 60–69 years; 367 (17%), ≥ 70 years. Prenatal 32–34 years
Follow-up time	33–35 years
Confounders evaluated?	It was noted that there was substantial variability among the study ophthalmologists in scoring small axial opacities and PSC changes
Description of results	There was an increase in axial opacities in the ≥ 100 -rad group for all age groups <70 years. Overall, 26.1% in ≥ 100 -rad group and 20.3% in controls had axial opacities. RRs: <40 = 13.8, 40–49 = 2.9, 50–59 = 2.7, 60–69 = 2.1, ≥ 70 = 1.4. Lesser PSC changes were also dose related. No dose-related differences were seen for cortical or nuclear opacities
Threshold dose (CI)	–
Prevalence at 1 Gy (95% CI)	–
Comments	Since they only screened those with ≥ 100 rad and unexposed, no dose–response relationship could be estimated. They used T65D dosimetry

Author and date	(M) Minamoto et al. (2004) (N) Nakashima et al. (2006)
Reference	(M) Minamoto, A., Taniguchi, H., Yoshitani, N., et al., 2004. Cataract in atomic bomb survivors. <i>Int. J. Radiat. Biol.</i> 80, 339–345 (N) Nakashima, E., Neriishi, K., Minamoto, A., 2006. A reanalysis of atomic-bomb cataract data, 2000–2002: a threshold analysis. <i>Health Phys.</i> 90, 154–160

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Type of study	Screening study within the atomic bomb AHS cohort
Number of individuals	(M) 873. (N) 701 (postnatal exposed only). Numbers were limited because ophthalmologists were only scheduled for a fraction of the daily AHS clinics, but individual doses are random with respect to particular clinic days
Ages at exposure	143 in utero, 501 aged 0–13 years, 229 aged >13 years (mean 8.8 years)
Gender distribution	61% females
Participation rate	93% examined
Dose	Mean 0.52 Sv, range 0–>2 Sv (DS02 dosimetry)
Radiation type	Gamma + neutron
Dose rate	Instantaneous
Technique for assessment	(M) Ophthalmoscopic and slit-lamp examination with pupil dilation, LOCS-II scores. Examinations by several examiners (and significant observer differences in PSC scoring were found, although observer restandardisation was repeated every 6 months and reported agreement was consistently >80%). Examiners blinded to dose obtained lens photographs. (N) Re-review of lens photographs by one ophthalmologist
Endpoints	Nuclear, cortical, and PSC opacities
Ages at observation	54–94 years, mean 64.8 years
Follow-up time	55–57 years
Confounders evaluated?	Participation rate did not vary by radiation dose. 23 questionnaire variables and 15 laboratory measures were evaluated for possible confounding. Adjusted for city, sex, age, and smoking
Description of results	Used proportional odds model (for graded responses), with adjustment for city, sex, age and smoking (N) The dose–response slope decreased significantly with increasing age at exposure ($P = 0.02$) (but this was also with increasing age at observation, so one cannot be sure which is the important variable) (N) No dose response for in-utero exposed ($P > 0.2$), but this may reflect lack of statistical power due to small numbers and smaller percentage with higher doses
Threshold dose (CI)	(N) Cortical opacities, 0.6 Sv (95% CI <0–1.2); PSC, 0.7 Sv (95% CI <0–2.8) (these analyses excluded in-utero exposed)
Prevalence at 1 Sv (95% CI)	(M) ORs for opacities: nuclear 1.12 (95% CI 0.94–1.30), cortical 1.29 (95% CI 1.12–1.49), PSC 1.41 (95% CI 1.21–1.64)
Comments	Somewhat difficult to interpret because the proportional odds models use the graded opacity scores with a fairly strong assumption that successive levels represent equivalent increases in ORs. The initial study (M) had some problems with variations between examiners in scoring, but (N) had a uniform scoring by one examiner and the results were very similar. Note: This was the first atomic bomb study to get away from classifying ‘axial opacities’, which were probably a mixture of nuclear, cortical, and PSC

Author and date	Neriishi et al., 2007
Reference	Neriishi, K., Nakashima, E., M inamoto, A., et al., 2007. Postoperative cataract cases among atomic bomb survivors: radiation dose response and threshold. <i>Radiat. Res.</i> 168, 404–408
Type of study	Ophthalmoscopic examination to determine cataract surgery prevalence in AHS cohort
Number of individuals	3761 who attended AHS clinic during 2000–2002
Ages at exposure	0 to >20 years: 21% aged 0–10 years, 48% aged 11–20 years, 31% aged ≥21 years
Gender distribution	Not reported, but approximately 60% females

Participation rate	All who came to the AHS clinic (~70% of those eligible)
Dose	0->3 Gy (previously called Sv)
Radiation type	Gamma + neutron
Dose rate	Instantaneous
Technique for assessment	Ophthalmoscopic examination to determine indication of cataract surgery
Endpoint	Surgically removed cataract
Ages at observation	55–94 years
Follow-up time	55–57 years
Confounders evaluated?	Analyses adjusted for city, sex, age, and diabetes mellitus
Description of results	479 (12.7%) persons with cataract surgery. Linear dose term was significant. Addition of dose-squared was not significant ($P = 0.99$) Analyses by restricted dose ranges: 0–1 Gy, OR 1.38 (95% CI 0.95–2.01, $P = 0.10$); 0–0.5 Gy not statistically significant (loss of statistical power – excluded 1200 persons and restricted dose range) While there were age by sex and age by city interactions, there were none with radiation dose, and the dose–response relationship was not affected
Threshold dose (CI)	Best estimate: 0.1 Gy (95% CI <0–0.8)
Risk at 1 Gy (95% CI)	OR 1.39 (95% CI 1.24–1.55)
Comments	Anatomical location of the cataracts was not characterised. This was the first substantial evidence that radiation doses of <1 Gy are related to clinically significant cataracts Models assuming neutron RBEs of 5, 10, 15, 20, and 25 were examined. An RBE of 10 provided a slightly better fit than the other models, but the differences were not substantial using the AIC criterion [Note: A limitation of these data is that they are prevalence data, but new not-yet-published data on the incidence of cataract surgery (1986–2005) also show a significant dose association and a low dose threshold]

NA, not available; PSC, posterior subcapsular; OR, odds ratio; CI, confidence interval; LOCS, Lens Opacity Classification System; ARS, acute radiation syndrome; UV, ultraviolet; HR, hazard ratio; IC, interventional cardiology; FLD, focal lens defects; RR, relative risk; AHS, Adult Health Study; RBE, relative biological effectiveness.

* Note: Otake et al. (1992) re-analysed this study using the DS86 dosimetry system, but the data they reported are so discrepant from the original (viz. 90% with axial opacities vs 26% in the original) that their re-analysis is not included here. (Ref: Otake, M., Finch, S., Choshi, K., Takaku, I., Mishima, H., Takase, T., 1992. Radiation-related ophthalmological changes and aging among Hiroshima and Nagasaki A-bomb survivors: a reanalysis. *Radiat. Res.* 131, 315–324).

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