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Early and late effects of radiation in normal tissues and organs: threshold doses for tissue reactions and other non-cancer effects of radiation in a radiation protection context

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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 of ICRP 103 (2007), and it provides updated estimates of 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, musculoskeletal, endocrine and nervous systems, the digestive and urinary tracts, the skin and the eye.

Particular attention is paid to circulatory disease and to eye cataracts, because of recent evidence of higher incidences of injury than expected after lower doses, and 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 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 ameliorate 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 modifying 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 which enhance radiation responses, notably other cytotoxic agents such as antimetabolites, alkylating agents, antiangiogenic drugs, antibiotics, as well as genetic and co-morbidity 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 very late reactions occurring after low total doses, such as for cataracts and for circulatory disease, it appears that the rate of dose delivery does not modify the incidence which implies that the injury in these cases is caused by single-hit 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.

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

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 ICRP Report 103 (2007), and the need for this was highlighted by reports in recent years of unexpected high incidences of eye cataracts and circulatory disease after low doses of radiation.

It was 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 were 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 was also considered with respect to compounds that either exacerbate or ameliorate radiation injury, and hence their ability to modify the basic threshold doses. It was intended to pay particular attention to recent information on eye cataracts and circulatory disease, where in both cases the threshold doses determined after long followup times appeared to be much lower than considered previously.

The membership of the Task Group was as follows:

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The membership of Committee 1 during the preparation of this report was:

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EXECUTIVE SUMMARY

(a) The Commission issued revised recommendations for a System of Radiological Protection in 2007 (*ICRP Publication 103*). This included consideration of the detriment arising from non-cancer effects of radiation on health. These effects have been called Deterministic Effects, and now they are recommended to be called 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*, high LET radiation in *Publication 58*, the skin in *Publication 59*, and the skin and the eye in *Publication 85*.

(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 (ICRP, 2007) that particular attention should be paid to radiation effects in the lens of the eye and in the cardiovascular system, because of recent published observations of radiation effects in these systems occurring after much lower doses than reported previously. 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 e.g. UNSCEAR (2006), were also taken into account.

(c) The main emphasis of the review was to provide estimates of threshold dose, defined 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 such estimates were unchanged because of a lack of new informative data, but other estimates required modification. Section 2 was devoted to individual organ systems, first to consider the human evidence and then to support that with evidence from pre-clinical experimental systems. Section 3 considered the various biological response modifiers that have been used to modify radiation responses. Then 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. Appendix A contains a series of Tables of critique for each of the earlier publications concerning radiation induced cataract, in order to provide a sound reference basis for the changes in recommended dose limits. Appendix B describes how excess risk relationships at low doses can be related to radiobiological models for tissue dose-response curves in the case of cardiovascular disease.

(d) Acute threshold doses of about 0.5 Gy, and chronic dose rates of 0.4 Gy per year, remain as recommended values for depression of haematopoiesis. Also, for mortality the threshold values of about 1 Gy acute dose (without medical care), and 2-3 Gy (with good medical care), are unchanged from previous ICRP values. Protracted doses of 4-8 Gy in 1 week or 10-14 Gy accumulated over 1 to 3 months, likely are tolerable.Growth factor administration is considered as beneficial to help

increase survival rates after radiation exposure of the bone marrow, and pre-clinical studies suggest that threshold doses might be increased up to double 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 about 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, as well as co-morbidities 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 to 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 previously recommended. For male fertlity, 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 pre-clinical studies, a variety of biological response modifiers has been investigated including hormonal manipulation, antioxidants, radical scavengers, and natural compounds, but at the present time there is no over-riding conclusion that would favour one compound versus others. In females, radioresponsiveness increases as age increases, because of the decline in the size of the oocyte pool with increasing age. 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.

(g) The salient features of the early and late radiation response 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 only the epidermis is irradiated or both epidermis and dermis. In humans, the most successful agents for reducing early reactions are anti-inflammatory compounds, and polyunsaturated fatty acids have shown promise in pre-clinical systems. For reducing late reactions, SOD, FGF, captopril, polyunsaturated fatty acids, α-tochopherol and inhibition of TGFβ signalling have shown some promise in both humans and pre-clinical systems, with dose modification factors of 1.1-1.2 and a maximum of about 1.5.

(h) Circulatory disease has not been previously 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. The evidence arises from radiotherapeutic experience and epidemiological studies following nuclear and other 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 about 0.5 Gy (or 500 mSv) 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, more than 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 particular emphasis is given to optimisation. However, it is emphasised that there are notable uncertainties in determining 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, ie. approximately 0.5 Gy.

(i) For cataracts in the eye lens induced by acute exposures, recent studies, where formal estimates of threshold doses have been made after long follow-up periods, indicate values around 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 generally had short follow-up periods, failed to take into account the increasing latency period as dose decreases, did not have sufficient sensitivity in detecting 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 around 0.5 Gy have been similarly deduced from recent studies. However, the evidence pertaining to the latter exposures refers mainly to opacities rather than to cataracts impairing vision, because the follow-up times are shorter in those studies. For chronic exposure over several to many years, again 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 per 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 ACE inhibitors had no significant effect.

(k) In the urinary tract, the kidneys are the most sensitive organ, the bladder and the ureters are more resistant (deduced from radiotherapeutic experience, with usually 5 years follow-up time). The threshold dose for the human kidney is about 7-8 Gy acute dose, and 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. Antiinflammatory agents have produced equivocal benefits in both human and animal systems. The most promising pre-clinical agents to date in reducing radiation nephropathy are ACE inhibitors and AII receptor antagonists. Pre-clinical 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 pathologies, namely 1) osteoradionecrosis, 2) spontaneous fractures or fractures with less than normal trauma, or 3) abnormalities of bone growth. The threshold dose for necrosis of femoral heads and fractures of ribs (after 5 years) is around 50 Gy in 2 Gy fractions, and about 55 Gy for skeletal muscle. In contrast to mature bone, growing bone is among the most radiosensitive of all tissues 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 per fraction. The hypothalamus is more radiosensitive than the pituitary. In children, radiation effects include growth hormone deficiency, precocious puberty (after lower doses) or delayed puberty (after higher doses), hypopituitarism, and hyperparathyroidism. In adults, radiation effects include hyperprolactinemia, hypogonadism, obesity, hypothyroidism, hyperthyroidism, and ACTH deficiency. Strategies for mitigating the effects of radiation on the endocrine system include growth hormone (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 gonadotrophin secretion after pituitary damage.

(n) The threshold dose for symptomatic spinal cord injury (myelitis) is about 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 lenth) 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 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 imparment in adult life detected after exposure to doses >100 mGy before 18 months. There are no recognised mitigating agents for use in humans to treat spinal cord injury after irradiation. Pre-clinical studies with anti-inflammatory agents, ACE inhibitors and AII receptor antagonists, some growth factors, and polyunsaturated fatty acids, have shown the most promise.

(o) This ICRP report has produced some changes to indicated threshold doses for tissue reactions, compared to those stated in ICRP 103. First, the threshold dose for radiation-induced eye cataracts is now considered to be around 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 around 0.5 Gy has been proposed for acute, and fractionated/protracted exposures, on the basis that this might lead to circulatory disease within a few percent of 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 makes 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 more than 10 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 around 100 mGy 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 higher than 500 mGy the risk of tissue reactions (deterministic effects) becomes increasingly important, in particular for the lens of the eye and the circulatory system at very long times after radiation exposure.

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 that same health effect.

Absorbed dose, D

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

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 sub-acutely to all or most of the body. It follows a dose dependent clinical course divided into prodromal, latent and manifest periods of illness.

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, 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.

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 a potentially controllable process.

Angiogenesis

Production of new blood vessels, mediated through tumour-angiogenesis factor (TAF).

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 nonself. 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 Arrythmias

Abnormally slow (brachycardia) 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.

Conditional renewing (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 the 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 not only hematopoietic cells but many other cell types as well.

Do

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 post-irradiation 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).

DMF

Dose modifying 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 in weeks to a few months after exposure (by definition within about 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 subjects irradiated (‘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, minus 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

Non-hierarchical cell populations in which function and proliferation take place in the same cells.

Flexure dose

Low-dose limit for effective fractionation; no detectable increase in isoeffect dose results when the fraction size is smaller than the flexure dose.

Fractionation

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

Fractionation sensitivity

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

FSU

Functional sub-units of tissues, e.g., nephrons in kidney, alveoli in lung.

Gastrointestinal (GI)

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 *versus* host disease (GVHD)

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

Granulocyte colony-stimulating factor (G-CSF)

Cytokine that stimulates differentiation of progenitor cells into granulocytes.

Granulocyte-macrophage colony-stimulating

factor (GM-CSF)

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) (GH)

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 cells, and postmitotic (differentiating or mature) cells.

565 High LET

566 Radiation having a high linear energy transfer, for example, alpha particles,
567 heavy ions and interaction productions of fast neutrons. The ionisation
568 density along the radiation track is high.

569 Hormones

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

572 Hyperbaric oxygen (HBO)

573 The use of high oxygen pressures (2–3 atmospheres) to enhance oxygen
574 availability in radiotherapy.

575 Hyperfractionation

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

577 Hypertrophic cardiomyopathy

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

580 Hypofractionation

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

582 Hypoplasia

583 Reduction in cell numbers in a tissue e.g. owing to radiation-induced
584 impairment of proliferation in early-responding tissues.

585 Immune system

586 The body's defense system which protects it from foreign substances such as
587 bacteria and viruses that are harmful to it.

588 Incidence (incidence rate)

589 The rate of occurrence of a disease in a population within a specified period
590 of time, often expressed as the number of cases of a disease arising per
591 100,000 individuals per year (or per 100,000 person-years).

592 Initial slope

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

595 Interphase death

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

598 Iso-effect plots

599 Doses for equal effect (e.g. ED_{50}) plotted against dose per fraction or dose
600 rate.

601 Late normal-tissue responses

Radiation-induced normal-tissue damage that in humans is expressed months to years after exposure (by definition later than about 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 (LET)

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

Linear-non-threshold (LNT) 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 excess cancer and/or heritable disease 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 one proportional to the square of dose (quadratic term).

Linear-quadratic (LQ) 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 CNS failure within 48 hours.

Low LET

Radiation having a low Linear Energy Transfer, for example 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 (M-CSF)

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 $SF = 1 - [1 - \exp(-D/Do]^n$.

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.

Non-cancer diseases

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

NTCP

Normal-tissue complication probability; generally a term 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 1) excluded exposures and exposures from exempt activities involving radiation or exempt sources; 2) any medical exposure; and 3) the normal local natural background radiation.

Oedema

Abnormal accumulation of fluid e.g. pulmonary oedema refers to a buildup of fluid in the lungs.

Pericarditis

Inflammation of the pericardium, the membrane that surrounds the heart, most frequently attributable to infectious agents but also well established 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 (PDGF)

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 hours following irradiation as a 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.

Prophylactic

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 (Dq)

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 hypothesized 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. SF_2) 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 isoeffective total dose with a decrease in dose per fraction or with irradiation at low dose rates.

Relative biological effectiveness (RBE)

The ratio of a dose of a low-LET reference radiation to a dose of the radiation considered that gives an identical biological effect. RBE 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 then 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, aging, 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 (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.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 permenant brain dysfunction. Two majors 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 isoeffective total dose for local tumour control or normal-tissue complications that follows a change in the overall treatment duration.

Tissue-rescuing unit (TRU)

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 of 1–5 per cent). Actual values depend on treatment protocol, irradiated volume, concomitant therapies, etc., but also on the status of the organ/patient.

Transforming growth factor (TGF-β)

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

Transit cells

Maturing 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.

References for the Glossary

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1. INTRODUCTION

1.1. Purpose of report

(1) The purpose of this report is to review 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. There will be an update of the information given in ICRP Publication 41 (ICRP, 1984), including new data on cardiovascular effects and the risk of radiation-induced cataracts. The influence of potential modifiers of the basic radiation sensitivity of normal tissues will also be considered with respect to compounds that either exacerbate or ameliorate radiation injury.

(2) The report that follows 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 various normal tissues (Potten and Hendry, 1983; UNSCEAR, 1988; Scherer, Streffer and Trott, 1991; Shrieve and Loeffler 2011), as well as for particular organ systems e.g. skin (Potten, 1985; ICRP, 1999), intestine (Potten and Hendry, 1995), bone marrow (Hendry and Lord, 1995), and the immune system (UNSCEAR, 2006). Instead, a critical evaluation of each of the various issues for radiation protection is provided, 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 effects of prenatal irradiation are not included because they were dealt with in ICRP Publication 90 (ICRP, 2003).

1.2. Definition and nature of tissue reactions to ionising radiation

(3) 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 on the sensitivity of the method used to detect it.

(4) 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 ICRP Publication 41 (ICRP, 1984). This was later considered an unsuitable term and in ICRP Publication 60 (ICRP, 1991) it was replaced by the term “deterministic”, meaning “causally determined by

preceding events". 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 ICRP Publication 60, 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 plays a crucial role in determining tissue response to radiation. This is further elucidated in section 1.3.7.

(5) 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 Chapter 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 extracellular matrix, which are common to most organs of the body.

(6) Early tissue reactions (hours to a few weeks after irradiation) may be of an inflammatory nature, occurring as a result of cell permeability changes and 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 coexist.

(7) 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 (FSU) 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. By 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).

(8) In this report, we define the term "*threshold dose*", or $ED_{1,}$ (Estimated Dose for 1% incidence) as denoting the amount of radiation that is required to cause a specific, observable effect in only 1% of individuals exposed to radiation (Figure 1.1). In the case of erythema of the skin, for

example, the ED_1 is about 5-6 Gy received in a single exposure, which is higher than the ED_1 for temporary depilation (4 Gy) but lower than the ED_1 for desquamation and necrosis (6-10 Gy), as will be discussed below (section 2.4). Hence, ED_1 is used to denote the minimum amount of radiation that is required to cause a specific tissue effect. 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 one percent. The 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.

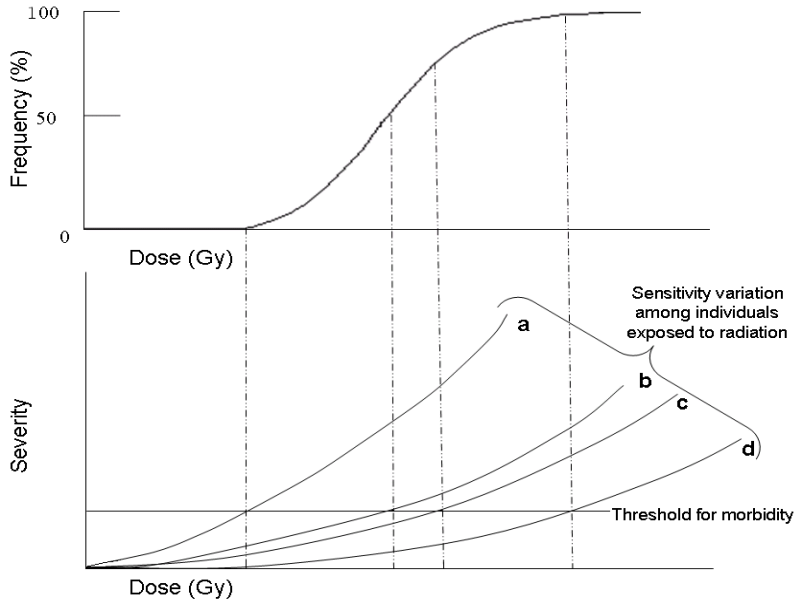

Fig. 1.1. Relationships between dose and the frequency or severity of tissue reactions. Upper Panel: The incidence (Frequency) of morbidity as a function of dose in a population of individuals of varying sensitivities. Lower Panel: The Dose versus Reaction Severity relationship for four subpopulations with different radiosensitivities ('a' being most radiosensitive, 'd' being least radiosensitive) comprising the total population. (Adapted from ICRP publication 60 (ICRP, 1991; Hendry et al., 2006)).

(9) 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 nearly all individuals. The term "clinically significant" is used to denote that 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 less than 1 % in the

case of induced paralysis, whereas it may be a few % 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 manifestations. 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 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 preoperative radiotherapy for rectal cancer (Jung et al., 2001).

1.3. General principles of radiation effects in cells and tissues

1.3.1. Cell survival

(10) 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 of 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.

(11) 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.

(12) For a given level of tissue damage in organs like 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.

(13) Since the ICRP 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 (Figure 1.2).

(14) In the LQ formula: $S = \exp-(\alpha D+\beta D^2)$, the constant α describes the linear component of cell sensitivity to killing on a semi-log plot of survival (log) versus dose (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 like 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, such as the 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 subpopulations with different sensitivities as a function of cell-cycle phase. The α/β ratio is generally in the range 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 repolulation of surviving cells with increasing total overall treatment time.

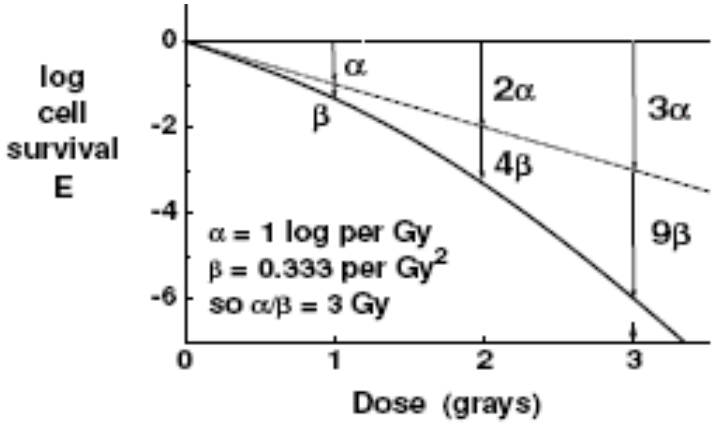

Fig. 1.2. Dose-response for cell survival (S) on a semi-log plot of (log S=E) versus dose, described by the linear quadratic equation $S = \exp - (\alpha D + \beta D^2)$ or $E=- (\alpha D + \beta D^2)$ (Fowler 2006). Alpha and beta are the coefficients of the non-repairable and repairable components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

(15) The half time for repair is generally 1-2 hours, 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 around 10 cGy per minute 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 less than 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 above 0.2-0.3 Gy, when there are sufficient induced DNA double strand breaks to trigger damage response signalling (Joiner et al., 2001). Hence this is a limitation on the use of LQ methodology down to 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 (Linear Energy Transfer) 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.

(16) 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 Dq (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

(17) Tissues vary widely in the rates at which their constituent cells are normally replaced and in the population dynamics through which the production, differentiation, aging, 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 post-mitotic 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.

(18) Other types of tissues do not have seperate regenerative stem cell populations. These tissues 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 long after irradiation. Far less

protection by regenerative or compensatory proliferation is to be expected during fractionated or protracted exposures in tissues of this type; e.g. the liver, where parenchymal cell renewal is low, or blood vessels, where endothelial cell turnover also is very low (Michalowski, 1981; Wheldon et al., 1982).

(19) 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.

(20) 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

(21) 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” (PLD) and “slow-repair”, may similarly contribute to an increase in survival. Cell replacement may also occur by migration of unirradiated cells from unaffected regions.

(22) 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 cytocidal effectiveness of a given dose when it is fractionated (UNSCEAR, 1982; Withers and Elkind, 1969).

Repair of Sublethal Damage

(23) 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; *i.e.* 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 the 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 is, the greater its potential for repair of sublethal injury.

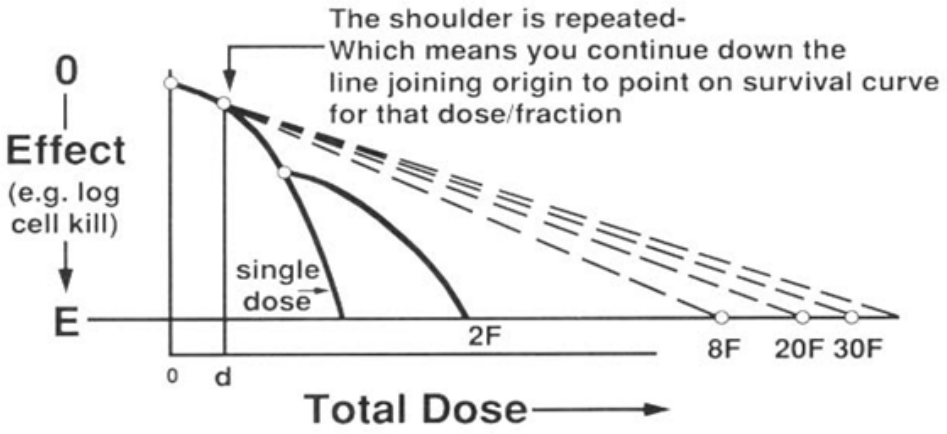

Fig. 1.3. The effective dose-response curve for a multifraction regimen approaches an exponential function of dose for many doses. The effective dose-response relationship is a straight line from the origin through the point on the single-dose survival curve corresponding to the daily dose fraction (typically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

(24) 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. As a dose is delivered in smaller and smaller increments, there is increasing repair between successive exposures and a progressively larger proportion of the total injury inflicted by each increment is in the form of sublethal damage, whereas an increasing proportion of the lethal injury results from non-reparable damage. Ultimately, however, a dose rate will be reached when all the sublethal damage is repaired and only lethal damage remains. This limiting dose rate, shown by the bold solid line in Fig. 1.4, is generally > 0.2 Gy min^{-1}. In this case the slope of the survival curve will be described solely by the α component. There is also a “reverse dose-rate effect” at a dose-rate where cells accumulate in the radiosensitive G2 phase of the cycle, and this sensitises the cell population slightly.

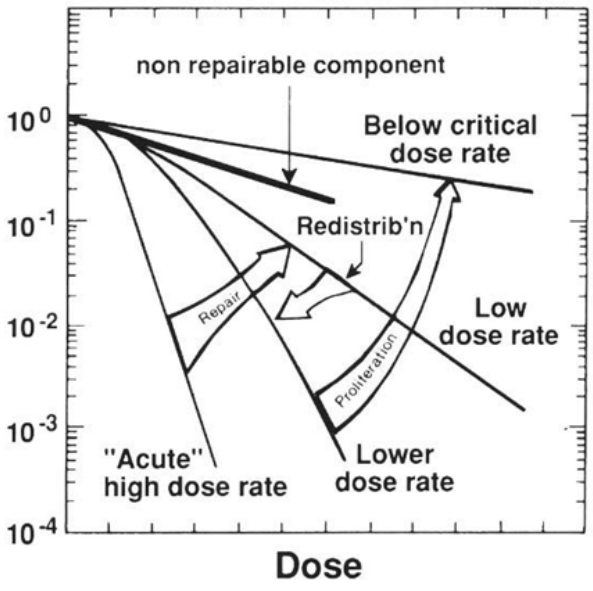

Fig. 1.4. The dose-rate effect resulting from repair of sublethal radiation damage, redistribution in the cycle, and cell proliferation. The dose-response curve for acute exposures is characterised by a broad initial shoulder. As the dose rate is reduced, the survival curve becomes progressively more 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 G2, a radiosensitive phase, but still cannot divide. A further lowering of dose rate below this critical dose rate allows cells to escape the G2 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 (Hall and Giaccia, 2006).

Repopulation

(25) 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 counterbalance 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^{-1} for a limited period of time (Quastler et al., 1959). In contrast, the more slowly proliferating testis of the dog can tolerate only 1.7 - 5 mGy day^{-1} when exposed daily for the lifetime of the animal (Casarett and Eddy. 1968; Fedorova and Markelov 1978, 1979).

(26) For tissues with low rates of cell proliferation, repopulation does not occur until much longer times 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

(27) Experimental animals and humans can tolerate higher total doses of chronic, low dose rate irradiation than acute single doses (Fliedner 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).

(28) Radioadaptation 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 exposures (Smirnova and Yonezawa, 2004). The induction of adaptive reactions decreases with increasing dose, and there is little effect above 0.5 Gy (Fliedner et al., 2002). There is scant evidence on the effects of adaptation in case of exposures to high-LET radiation.

(29) 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, e.g. 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 G_1 and G_2 checkpoints, induction of protein synthesis, stimulation of cell proliferation and activation of radioprotective systems, e.g. endogenous stress proteins or antioxidants (Ikushima et al., 1996; Nogami et al., 1993; Seed et al., 2002). Glutathione produced in cells after exposure to small doses of radiation also exerts a stimulating effect on immune reactions (Kojima et al., 2002).

(30) Chronic radiation syndrome (CRS) is a clinical syndrome which develops in man after whole body annual radiation exposures exceeding 0.7 – 1.0 Gy and cumulative doses > 2-3 Gy over 2-3 years (Barabanova et al., 2007). CRS is characterised by inhibition of haemopoiesis and immune reactions, structural and functional disorders of the central-nervous, cardiovascular and other organ systems. The severity of these effects is determined by exposure dose rate and total dose. The cessation of exposure to ionising radiation allows repair processes to occur, 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 (Akleyev and Kisselyov 2002; Okladnikova et al., 1992, 1993, 1994).

1.3.4. Iso-effect relationships

(31) Efforts to quantify the relationship between the severity of tissue damage, the 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 apply only 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 ED_1 doses for chronic exposures, as may occur after an accident.

(32) 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 a 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 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) (Barendsen, 1982; Withers et al., 1980). 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 (Steel, 2002; Thames and Hendry, 1987).

(33) The effects of increasing treatment time can be taken into account by allowing for the potential doubling time Tpot of a tissue after a lag period or "kick-off time" Tk:

$E = nd(\alpha + \beta d) - (T - T\kappa)(\log_e 2)/Tpot$

$E/\alpha = nd(1 + d/(\alpha/\beta)) - (T - T\kappa)(\log_e 2)/\alpha Tpot)$

BED (Biological Equivalent Dose) is E/α, and is the equivalent total dose delivered at very low dose-rate, or using very many small fractions delivered at high dose rate, i.e. n x 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 (Dprolif), varies amongst renewal tissues and can be as high as 0.8 Gy per day for mucosa after a lag period of less than 12 days when using 2 Gy daily doses (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).

(34) 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. BED 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.

(35) Since 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.

(36) 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 (LET)

(37) 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 (PLD) and "slow repair" also decrease with increasing LET. As a result of each of these factors, the RBE (relative biological effectiveness) of high-LET radiation increases with decreasing dose or dose per fraction (Field and Hornsey 1979) (Fig. 1.6), tending to become constant only at low doses (<0.5 Gy) and low dose rates (<0.2 Gy min^{-1}), where only single-hit events are effective. These considerations also apply for carbon ions, which have about the same RBE as fast neutrons, but 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).

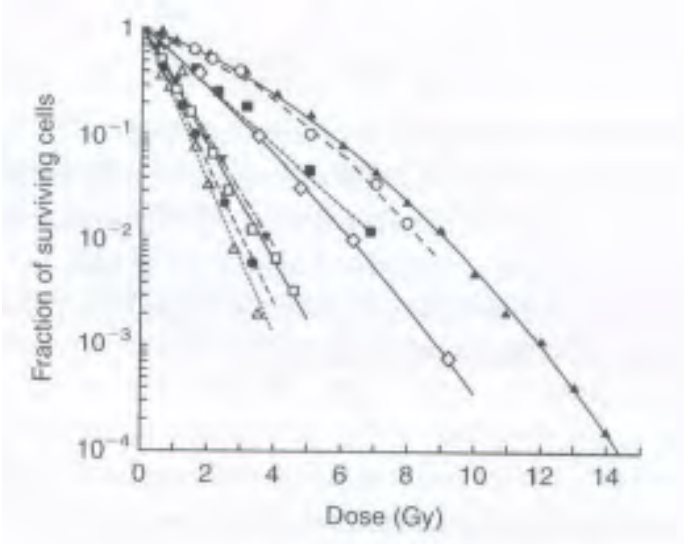

Fig. 1.5. Survival curves for human kidney cells exposed in vitro to 200 kV x rays (▲) or radiation of increasing LET (reproduced from Barendsen, 1968).

□ *2.5 MeV α particles ; 165 keV/μm*
Δ *4.0 MeV α particles ; 110* keV/μm
• *5.1MeVαparticles ; 88*keV/μm
▼*8.3 MeV α particles ; 61* keV/μm
◊ *26.0 MeV α particles ; 25* keV/μm
■ *3.0 MeV α deuterons; 20* keV/μm
O *14.9 MeV α deuterons ; 5.6* keV/μm

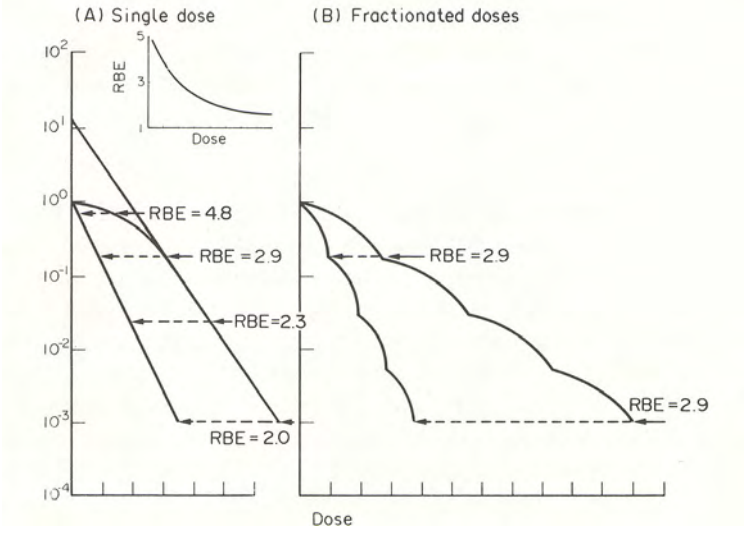

Fig. 1.6. Typical survival curves for mammalian cells exposed to x rays or fast neutrons. A. Single Doses. With x rays the survival curve has a large initial shoulder; with fast neutrons the initial shoulder is smaller and the final slope steeper. As a result of the differences in shapes the RBE is large for small doses, decreasing with increasing dose, as illustrated in the inset diagram. B. Fractionated Doses. The effect of giving 4 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 4 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 publication 41, 1984).

(38) 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) versus early reactions in other tissues (e.g. haemopoietic tissue, skin) are shown in Figure 1.7. These aspects and many other details of the RBE for tissue reactions (deterministic effects) have been described (ICRP, 1990).

1.3.6. Partial organ irradiation

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

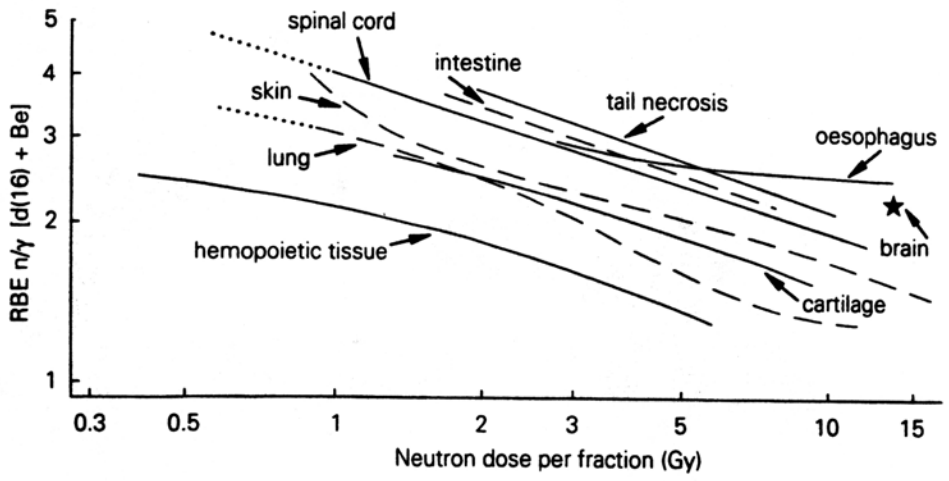

Fig. 1.7. RBE as a function of neutron dose per fraction for different normal tissues. (Field and Hornsey, 1979).

(40) Paired organs, like kidneys or salivary glands, and organs in which the functional subunits (FSUs) are arranged in a parallel way, e.g. 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 about 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.

(41) By contrast, organs like 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 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.

(42) 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 probablility 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’ (Kallman et al., 1992; Withers et al., 1988). 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 take into account 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 (Marks et al., 2010; Ten Haken, 2001).

1.3.7. Non-cytocidal radiation effects

(43) 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 on 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 and nitrogen species (ROS, RNS) 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 post-mitotic 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 (Bentzen, 2006; Brush et al., 2007; Denham et al., 2001). These tissue reponses, 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.

(44) 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 toward the end of a treatment course differs substantially from the normal tissue that was irradiated in the beginning (Denham and Hauer-Jensen, 2002).

(45) 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: 1) cytocidal radiation effects (target cell death by clonogenic cell death and/or apoptosis); 2) functional (non-cytocidal) radiation effects; 3) secondary (reactive) effects (Denham et al., 2001).

1.3.8. Heterogeneity in response

(46) 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. Very few individuals (much less than 1 %) are homozygotes for mutations in critical repair genes and are consequently 2-3 fold more sensitive than the average. 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 co-morbidities, such as the greater responses observed in HIV individuals. These effects are described in the chapters 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

(47) 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 (BM) and thymus along with secondary and tertiary lymphatic tissues. The haematopoietic stem cell (HSC) is central to the maintenance of steady state haemopoiesis and thymopoiesis, as well as multilineage reconstitution after radiation-induced myelosuppression. Most of the HSC are found in the BM niche, however they continue to migrate via the blood stream 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 BM-derived early T cell progenitors and/or HSCs for continued production of new T cells.

(48) Haematopoiesis generates all blood cell lineages from privileged sites (niches) located within the BM and thymus (Ladi et al., 2006; Scadden, 2006). To maintain haemostasis an adult produces approximately 2×10^{11} erythrocytes, 1×10^{11} leucocytes 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).

(49) 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 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; Ladi et al., 2006; Scadden, 2006; Zhu and Emerson, 2004). It is likely that vascular, perivascular and endosteal cells contribute to specialised or common BM 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 physiologic challenge (Fuchs et al., 2004; Scadden, 2006). Although the vast majority of HSC in the adult are located in the bone marrow, HSC circulate freely, albeit at very low numbers. These HSC, 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 HSC are unclear. They may provide a readily accessible source of HSC and/or home back to the marrow niche and further influence HSC behavior and physiologic status. HSCs can regenerate the entire haematopoietic and immune systems, whether under homeostatic pressure or after to cytotoxic chemotherapy or radiation. A fundamental question is how these niches affect maintenance and regeneration of HSC and progenitor cells under steady state conditions versus those after radiation-induced depletion.

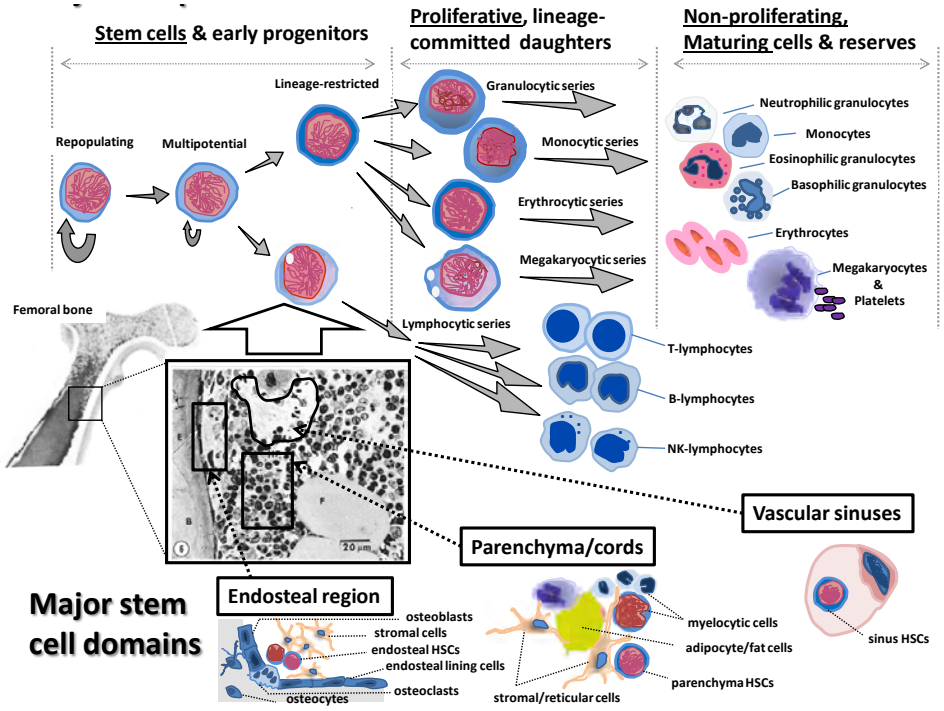

Fig. 2.1. General features of hematopoietic tissues. Their primary activity is the manufacture of various species of mature, functional cells that circulate in the blood. The bone marrow is an hierarchical, self-renewing, amplifying tissue, driven by small numbers of stem cells and early progenitors 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. Hematopoietic stem cells reside within three domains: i) endosteal; ii) parenchyma cord; and vascular sinus regions. The figure shown was conceptually derived from a NIH online report (NIH Report 2008) and modified by Dr. Tom Seed, Bethesda, USA.

(50) The bone marrow and the thymus are the central haematopoietic and lymphoid tissues responsible for production of nearly all lymphocytes (UNSCEAR, 2008). All cells of the immune system originate from BM-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 NK cells are produced within specialised niches within the BM, whereas early thymic progenitors leave the BM 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 (T reg), gamma/delta T cells and natural killer (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 recently proposed. (Steinman, 2007; Iwakura. and Ishigame, 2006). 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 TNF but not Ifn-gamma. 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, Peyers 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 defense and its resident T cells are called intestinal epithelial lymphocytes (IEL).

2.1.2. Acute radiation syndrome (ARS): Haematopoietic effects

(51) 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 (HGF). (UNSCEAR 1988; Anno et al., 1989, 2003; Baranov 1996; Waselenko et al., 2004). The data from available sources are listed in Table 2.1**.**

The LD50/60 for Humans Exposed to Acute Ionising Radiation

(52) Lethality after total-body radiation exposure is dose and dose rate dependent. Reviews of the cumulative data on human radiation exposure suggest that the $LD_{50/60}$ (50% lethal dose at relatively high exposure rates assessed at 60 days after exposure) is approximately 3.3 to 4.5 Gy in the absence of medical management and 6 to 7 Gy when medical management, consisting of antibiotics, blood products, fluids, anti-diarrhoe compounds, nutrition *etc* is provided (UNSCEAR Annex G, 1988; Anno et al., 1989, 2003; Baranov, 1996; Waselenko et al., 2004). No HGF (haematopoietic growth factors) 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 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 1996; Baranov and Guskova, 1990). These responses emphasise the value of medical management as the standard of care for severely irradiated personnel.

Summary of anecdotal data

(53) 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 radiation accident victims 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 LD50/60. The combined presence of other non-haematopoietic sequelae may complicate the treatment paradigm and worsen the potential for survival.

1741

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	NumberExposed/ Estimated Exposure	Treatments	Reference
15-kiloton nuclear device	Hiroshima, 1945	N=150,000 casualties and 75,000 fatalities, all survivors < 300 cGy	Medical management	Shimizu et al., 1992
Nuclear Reactor	Chernobyl, 1986	N=214 with exposure 100- >1300 cGy	Medical management	Baranov, 1996; Fliedner et al., 1996; Georges and Storb, 1997
^{137}Cs radiotherapy unit	Goiania, Brazil, 1987	N=10, total body doses 250 - 700 cGy	GM-CSF Immunex, 500 μg/m^2/d, i.v.	Butturini et al., 1988
^{60}Co medical steriliser	San Salvador, 1989	N=3, 3-10 Gy total body with localised exposures (feet, legs) 2000 cGy, in 2 workers	GM-CSF Leukine, 240 μg/m^2, i.v.	Rafael-Hurtado et al., 1996
^{60}Co source	Istanbul, Turkey, 1998	N=10, 0.7-4.0 Gy protracted doses	G-CSF Neupogen 5 μg/m^2/d	IAEA, 2000
^{60}Co from atomic reactor	Israel, 1990	N=1, > 1000 cGy	IL-3 and GM-CSF after BMT	Nagler et al., 1996
^{60}Co	Nyasvizh, Belarus, 1991	N=1, 1200 - 1500 cGy	GM-CSF early (d 3-6) then IL-3 and GM-CSF (d 6-31)	Baranov et al., 1994
mixed neutron:γ radiation	Tokaimura, Japan, 1999	N=3, 800-1300 cGy	Stem cell Transplant, G-CSF, Epo, Tpo	Chiba et al., 2002; Nagayama et al., 2002
^{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 ug/m2/d), Epo (120U /kg/d)	Liu et al., 2008
^{192}Ir - source	Yanango, Peru, 1999	N=1, total body <300 cGy, 8000 cGy to right thigh	G-CSF (300 μg/day)	Zaharia et al., 2001
Teletherapy Head ^{60}Co	Samut Prakarn Province, Thailand, 2000	N=10, ≥ 200 cGy (4 received > 600 cGy)	G-CSF (lenograstim, 10 μg/kg/d) and GM-CSF (300 μg/d)	Jinaratana 2001

NOTE: In all of the above, where colony-stimulating factors were administered, medical management was also provided.

1742 *Pathophysiology of Lethal Radiation Exposure*

1743 (54) A single, lethal radiation exposure of animals and humans leads to the
1744 acute radiation syndrome (ARS) (Anno et al., 1989; Baranov et al., 1988). The
1745 haematopoietic system is the organ system that is most sensitive in the ARS.
1746 Clinically recognisable signs of the haematopoietic syndrome (ARS-HS) can be
1747 observed after radiation exposures of 2 to 10 Gy. Radiation-induced
1748 myelosuppression results in a transient or prolonged period of neutropenia,
1749 thrombocytopenia and lymphopenia, as a consequence of a dose-dependent
1750 level of killing of haematopoietic stem 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 HSC and seeding of a competent thymus.

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

(56) In the setting of neutropenia and thrombocytopenia, death from infectious complications and haemorrhagic events generally occurs within 14-28 days after irradiation. Treatment efficacy in terms of survival is dependent on protecting and/or enhancing recovery of the haematopoietic stem and progenitor cells, so that production of mature, functional neutrophils and PLTs 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 et al., 2005).

(57) Immune suppression is also a common problem consequent to high dose, total body irradiation similar to that noted with multiple cycle chemotherapy or myeloablative conditioning prior to stem cell transplant. The significant delay, for up to one 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 ARS

(58) 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 or stem cell transplantation (Baranov et al., 1988; Densow et al., 1997; Fliedner et al., 1996; Georges and Storb, 1997). This data-base 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.

(59) It has been suggested (Baranov et al., 1988; Baranov, 1996) that the most relevant parameter correlating with radiation dose causing severe ARS, after relatively uniform total body irradiation (TBI), is the day on which peripheral blood absolute neutrophil count (ANC) decreased to 500/μL (d500). If the patient had a d500 $\leq$ 14, this corresponded to a total body exposure of 5-6 Gy leading to very severe myelosuppression. Before Chernobyl, only 6 known ARS patients with severe myelosuppression and medical management demonstrated immediate recovery of haematopoiesis. The d500 of 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 total body exposure up to 8 Gy. Evaluation of neutrophil recovery curves from 18 patients who received estimated TBI doses of 4.7 to 8.3 Gy showed that levels of ANC < 100/μL were observed within 1-4 days after the respective d500 (Baranov et al., 1988; Baranov, 1996). It was also noted that fever and infection coincided exactly with neutropenic periods after doses of 4-5 Gy, and that these signs were more "aggressive" in all patients after 5-6 Gy. These data underscore the need for prophylactic administration of antobiotics when the d500 estimates a relatively uniform lethal exposure and the ANC continues to decrease towards severe neutropenia when patients are at the highest risk of sepsis.

Lessons learned

(60) 1) The d500 correlates well with the dose of a relatively uniform TBI and indicates that the time to d500 for radiation exposure≥ $LD_{50/60}$ (6 Gy) is 9-14 days. 2) All patients irradiated in the potentially lethal 4.7-8.3 Gy range experienced an ANC < 100μL within 1-4 days after the d500. 3) 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. 4) No haematopoietic growth factors were administered to these patients, emphasising the value of appropriate medical management in allowing for sufficient time for recovery of haematopoiesis to occur spontaneously. 5) 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 one and three months (UNSCEAR, 1988). Several models and formulae were proposed for describing the change in tolerance dose with increased fractionation and protraction of the irradiation, but the human data remain scarce.

2.1.3. Haematopoietic effects of chronic exposure

Clinical data

(61) 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 γ-radiation at dose rates below 0.25 Gy/year and cumulative doses from 1.0 to 1.5 Gy, showed no evidence of reduced haemopoiesis. 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 leucopenia. The highest total doses of 2-9 Gy resulted in leucocyte and thrombocyte counts of 50-65% of the baseline level. Some of these workers were also exposed to ^{239}Pu aerosols, giving estimated absorbed doses to the red bone marrow (RBM) of 0.01 to 45 cGy. Reduced lymphocyte counts were

noted at annual doses above 2.0 Gy and cumulative doses >6.0 Gy (Pesternikova and Okladnikova, 2003)

(62) Termination of exposure was followed by gradual normalisation of leucocyte counts, to 80-85% of baseline by the fifth year and to 88-95% by the 20^{th} -25^{th} year. However, even 40 years after exposure leucocyte counts were still only 88-95% of the baseline level. Leucopenia at 40 years after exposure was more prevalant after cumulative RBM doses of >2.0 Gy. Five years after termination of exposure to radiation, platelet counts were restored to normal in workers with cumulative doses below 6.0 Gy. For workers with higher cumulative doses, normalisation of platelet counts took up to 10 years (Pesternikova and Okladnikova, 2003).

(63) At 35-40 years after exposure to cumulative doses of 2-9 Gy (annual doses above 1.0 Gy), moderate bone marrow hypoplasia was still seen in 7% of Mayak workers (Okladnikova and Guskova, 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 per year, although no dose dependency was seen for BM hypoplasia at late 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).

(64) Persistent reductions in platelet and leucocyte counts were also registered in Techa riverside residents, exposed for many years to combined external γ- and internal radiation, mainly ^{90}Sr, at BM dose rates of >0.3-0.5 Gy per year (Akleyev et al., 1999; Akleyev and Varfolomeyeva 2007; Akleyev and Kisselyov, 2002).

Preclinical data

(65) 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 (LD/LDR) radiation exposure. This is due to increased rates of cell production resulting from shortening of the cell cycle and maturation time (Gidali 2002; Grigoryev et al., 1986), increased proliferative activity of stem cells and precursor cells (Muksinova and Mushkachyova, 1990), and stimulation of haemopoiesis (Fliedner et al., 2002; Lord, 1965). Increased repair of sub-lethal lesions also occurs in bone marrow precursor cells (Seed et al., 2002).

(66) 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 in excess of 0.075 Gy/day, nearly 60% of the irradiated dogs died from progressive aplastic anaemia in less than 300 days. The remaining dogs exhibited a remarkable adaptability to LD/LDR exposure. In the initial period (50-150 days) the animals showed a progressive decline of bone-marrow precursor cells, leucocytes 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. Leucocyte 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).

(67) Chronic irradiation of dogs to doses of 0.62 to 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).

(68) Rats and mice exposed to long-term irradiation at doses of 0.01 to 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 like erythropoietin, leucopoietin and thrombopoietin, which stimulate haematopoiesis and contribute to accelerated differentiation of committed cells and proliferation of stem and progenitor cells (Kaspar and Seed, 1984).

(69) The key factor triggering haemopoietic recovery is depletion of the stem cell compartment. Recovery and restoration of haemopoiesis 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).

(70) The haematopoietic microenvironment, 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 haematopoietic stem cells from bone marrow to the spleen, liver and lymph nodes can also occur. Recovery of haematopoiesis is more complete after exposure at low-dose-rate than at high-dose-rate. For example in mice, recovery of haemopoietic and stromal progenitor cells was almost complete by one year after 12.5 Gy delivered at 0.0005 Gy/minute compared with incomplete recovery after only 6.5 Gy given at 0.7 Gy/minute (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 BM

function (Fliedner et al., 2002; Seed et al., 1982). Immune and vascular disorders play an important role in this fibrotic development (Wynn, 2008).

(71) 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 leucocytes. Reduced numbers of erythrocytes were seen only in animals with daily intakes >185 kBq/day. The haemoglobin level was within normal limits over the entire experiment. However, animals given doses of 37 kBq/day had reduced BM 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 (CRS)

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

(73) The first clinical sign of CRS is a deficiency in haematopoiesis, which predominantly manifests as reductions in blood leucocyte and platelet counts and bone-marrow hypoplasia (Guskova and Baysogolov, 1971). Initially, the number of leucocytes is typically reduced to 40-65% and the platelets to 50-60% of the baseline level (Okladnikova et al., 2002). Leucopenia 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 leucopenia.

(74) In mild cases of CRS, 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 over 4.5 Gy/yr and total doses above 8 Gy (Guskova et al., 2002).

(75) Haematopoietic changes seen in CRS are usually accompanied by changes in the immune, nervous, cardiovascular, musculoskeletal systems and in the gastrointestinal tract. Reduced resistance to infection and allergic changes in the organism are characteristic of the development of CRS (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 demyelinisation, frequently of a transient nature, which appears to be dependent on vascular damage and certain metabolic disorders (Guskova et al., 2002; Guskova, 2000). CRS may also manifest as dysfunction in other organs *e.g.* reduced secretary 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

(76) A detailed description of radiation effects on the immune system was published by UNSCEAR (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, post-exposure 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).

(77) Immunosuppression occurs after whole body chronic irradiation at high doses and it may be observed at long times post-irradiation (Kirillova et al., 1988; Okladnikova 2001; Pecaut et al., 2001). Localised doses can also result in systemic immune suppression. The mechanisms involved include: radiation induced apoptosis of immunocompetent and progenitor cells, a shift in homeostasis balance between Th1 pattern (cell mediated immunity) and Th2 partten (humoral immunity) towards a pro-inflamatory profile, radiation-induced mutations in TCR genes, bystander effects and genomic instability. Ionizing 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 (UNSCEAR, 2006; Yagunov et al., 1998). Long-term recovery of a functional immune system depends upon concurrent recovery of the marrow-derived haematopoietic stem cells that serve as the source of early thymic progenitors (Guidos 2006; Schwarz and Bhandola, 2006).

(78) 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 natural killer cells (NK) 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).

(79) 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 < 0.05 Gy (Malyzhev et al., 1993; Pandey et al., 2005; Safwat, 2000). Evidence for similar effects on the human immune system is scarce. Data from animal experiments have shown that low-dose total-body irradiation (TBI) could enhance the immune response through: augmenting the proliferative response of the T-lymphocytes to mitogenic stimulation, altering cytokine production (particularly INF-γ and 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).

(80) 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

(81) Although few data are available on effects of low dose exposure in humans, some of them suggest that chronic exposure can induce a response of the innate immunity. 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 content of lysozyme in their saliva (Akleyev and Kossenko, 1991; Akleyev and Kisselyov, 2002). Reduced levels of components of C3 and C4 complements were also seen in radiology workers exposed for a period of over 5 years at dose rates below 3.5 mSv/year (Godekmerdan et al., 2004). Eight years after the accident at Chernobyl atomic power station, residents of contaminated areas exhibited decreased levels of NK cells and cleanup workers exposed to doses 10-30 cSv developed a dose-dependent reduction in the synthesis of leucocytic interferon and the C3-component of the complement (Asfandiiarova et al., 1998; Semenkov et al., 1997). However, under occupational LD/LDR exposure no effects of irradiation on the levels of NK cells were observed (Tuschl et al., 1990).

(82) Experiments on rodents confirmed that innate immune factors may change considerably following chronic irradiation. Low dose radiation exposure enhanced the phagocytic activity of macrophages (total dose of 200 mGy; dose rate 40 mGy/d) (Pandey et al., 2005) and secretion of IL-12 by peritoneal macrophages (75 mGy) in mice (Liu et al., 2003). NK-cells are relatively radioresistant. LDR γ-irradiation (10 cGy/year) of mice resulted in increased CD49+ NK-cells in the spleen at 28 and 32 weeks, while no changes occurred in NK cell activity (Lacoste-Collin et al., 2007). Moreover, activity of NK splenocytes increased in whole-body γ-irradiated mice (0.5 Gy) 2-6 hours after irradiation, due to induction of endogenous glutathione (Kojima et al., 2002).

Acquired immunity

(83) Prolonged exposure of humans, even at low doses, may induce dose-dependent decrease of 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) (Asfandiiarova et al., 1998; Vykhovanets et al., 2000; Yarilin, 1996). As in the atomic bomb survivors (Hayashi et al., 2003), a preferential CD4+ cell deficiency was observed many years after the Chernobyl accident. Proliferative response to mitogens was also altered. Dose-dependent reductions in CD4+, HLA-DR+ lymphocytes and the CD4+/CD8+ cell ratio were also obtained in the follow-up studies of residents of radioactive buildings for 2-13 years at a mean chronic dose of 169 mSv (Chang et al., 1999). The dynamics of post-irradiation 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).

(84) 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 γ-radiation at accumulated doses above 4 Gy (Okladnikova, 2001).

(85) 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 IgE level (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 in the number of circulating B-cells was seen (Rees et al., 2004). Moreover, there was a decrease in the level of immunoglobulins (IgA, IgG, IgM) (Godekmerdan et al., 2004).

(86) In addition, continuous LD γ-irradiation (10 cGy/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 γ-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 was associated with the cyclic recurrence of suppression and recovery processes in the thymus (Sergeyevich and Karnaukhova, 2002).

Immune reactions to internal irradiation

(87) Studies in rodents showed that internal irradiation with tritium led to more pronounced and prolonged immune depression than external γ-radiation at similar total doses, due to more severe damage to the lymphocyte precursors. Experiments using mice demonstrated that a prolonged exposure to tritium at cumulative doses of 0.2-1.0 Gy (dose rates 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 at late times after irradiation are 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).

(88) 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 i.v. injection of ^{239}Pu, giving skeletal doses > 3 Gy and 14 Gy inhibited humoral immunity (Kirillova et al., 1991). Exposure to ^{90}Sr at dose rates to RBM > 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

(89) Haematopoietic stem 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 sub-lethal 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 characterized 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 ionizing radiation has been associated with impairment of the immune system, and late effects (cancer and non-cancer diseases).

(90) 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

(91) 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 (GI) 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, 2005).

(92) It was previously believed that the severity of radiation injury in the gastrointestinal tract depends only 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.

(93) 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.

(94) 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.

(95) The liver is the largest internal organ of the human body. It plays a critical role in body metabolism, for example, glycogen storage, plasma protein synthesis, production of coagulation factors, detoxification, and production of bile. It is located in the right upper abdomen. 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 few organs in the body that is capable of regeneration. Hence, hepatocytes are considered unipotential stem cells (or reverting post-mitotic 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.

(96) The epithelial lining of the intestine covers an area roughly 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 done 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 in the order of 12-13 hrs, whereas the cell cycle time for crypt stem cells is considerably longer at approximately 24 hrs. The total transit time for cells from the crypt base to the villus tip is about 6-8 days and it takes 48-72 hrs 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 about 30 hrs, i.e. about 2.5 times that in mouse intestine (Kellett et al., 1992).

(97) Acute radiation injury to the intestine manifests within days of the first radiation 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 crypt cell cycle times may be as short as 6 hours (Lesher and Bauman, 1969). Stem cell doubling times are longer, up to about 24 hours, because of the concomitant division of stem cells and their loss to the differentiation pathway (Potten et al., 1988).

(98) The relative importance of clonogenic death versus 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 exposure doses

Oral mucosa and oesophagus

(99) 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 recently appreciated. 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.

(100) 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 above 50 Gy (using 2 Gy per fraction) but chronic ulcers usually do not occur with fractionated total doses < 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.

(101) 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.

(102) 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 to 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).

(103) 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 about 40-45 Gy total dose in 2 Gy fractions. Because the incidence of endoscopic changes is low and motility and transit times generally do not 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., 1996). 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

(104) 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 >1 Gy. As with oral mucositis, it is not appropriate to view intestinal radiation mucositis as solely 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 histopathologal 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.

(105) 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 toward 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.

(106) Delayed radiation injury of the gastro-intestinal tract occurs at least 3 months after radiation therapy, but usually several months or years after exposure. Common manifestations of delayed GI 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; Larsen et al., 2007; Regimbeau et al., 2001; Silvain et al., 1992).

(107) 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 (Denham et al., 2000; Hauer-Jensen et al., 1983, 1985; Travis and Followill 1991; Wang et al., 1999) showed that acute injury indeed 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).

(108) 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 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 post-radiation intestinal dysfunction seek medical attention. After radiotherapy of abdominal tumours, chronic symptoms or signs of intestinal dysfunction are present in 60–90% of patients (Fransson and Widmark 1999; Yeoh et al., 1993), 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.

(109) 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 (Hovdenak et al., 2000; Yeoh et al., 1998). 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., 1996, 2000, 2004).

(110) Androgen therapy of prostate cancer appears to influence both acute and chronic radiation proctitis (Peeters et al., 2005; Sanguineti et al., 2002). 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 in excess of 70 Gy (in$\leq$ 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

(111) While the acinar cells of the parotid gland are serous, the other two major salivary glands (the submandibular and sublingual) are mixed, *i.e*. they contain both serous and mucinous acinar cells. 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 (Cooper et al., 1995; Franzen et al., 1992). 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).

(112) 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.

(113) Turnover of hepatocytes is normally slow and acute radiation injury of the liver thus does not reflect clonogenic cell death. Rather, radiation-induced liver disease typically presents sub-acutely, about 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 the entire 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, 2010; Pan et al., 2010). If only one third of the liver is exposed then the dose for a 5% incidence of damage increases to > 42 Gy and if less than 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).

(114) 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 applied only 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, 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

(115) A substantial body of experimental work has been performed to investigate time-dose-fractionation relationships in the 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 (Fowler, 1989; Thames and Withers 1980). By 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).

(116) 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, 1995b).

(117) 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; Hauer-Jensen et al., 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 hrs 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 toward the end of the radiation schedule, after the onset of compensatory proliferation, rather than at the beginning (Allgood et al., 1996).

(118) Many mechanistic studies have been performed to reveal potentially important information about the radiation response of gastrointestinal tract organs. Several of these 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 (TGFβ) in radiation fibrosis was obtained in a model of radiation-induced bowel injury (Zheng et al., 2000).

(119) A particularly interesting debate evolves 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 total body irradiation (Paris et al., 2001). Because endothelial cell apoptosis, but not apoptosis of the crypt epithelium, is sphingomyelin-dependent, 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 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.

(120) 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 endothelial cells in these studies was increased by ~3.3 fold compared to the total body dose. The authors reported no marked endothelial cell apoptosis identified using TUNEL and caspase-3 positivity at 4-8 hours after 1 to 33 Gy delivered using this new approach or low LET radiation. 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 radiation-induced 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 GI epithelium did not protect mice from developing the GI radiation syndrome. In contrast, selective deletion of p53 from the GI epithelium, but not from endothelial cells, sensitised mice to the acute GI radiation syndrome. These authors conclude that the GI radiation syndrome is caused by death of GI epithelial cells and that the cells die by a mechanism that is independent of apoptosis, but regulated by p53.

(121) It is well known from other areas of gastrointestinal pathophysiology that genetic manipulations or pharmacologic 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 (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 and colleagues (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 total body radiation exposure

(122) In most total body radiation 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 total body irradiation 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 in excess 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 microorganisms (usually enterobacteriaceae) is an important cause of death after radiation doses in the "haematopoietic" dose range.

(123) The prodromal symptoms seen after total body irradiation 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 symtoms should be used with caution for predicting the radiation dose received by undividual 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.

(124) Survival is extremely unlikely with the full-fledged total body irradiation-induced gastrointestinal radiation syndrome. The gastrointestinal radiation syndrome develops after doses in excess of 6 Gy in humans, and 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 bacteremia 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.

(125) 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, for example, 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 among 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 (MODS) has been described (Monti et al., 2005).

(126) Information on non-cancer disease incidence and mortality is also available from cohorts of atomic bomb survivors (Preston et al., 2003; Shimizu et al., 1999; 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 interleukin 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

(127) 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. An extensive treatise of the internal exposure to radiation has recently been published in ICRP Publication 100, and the reader is referred to that publication for further details (ICRP, 2005).

(128) 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 (LD50/10 endpoint), the LD_{50} for ingestion of beta emitters, such as $^{106}Ru/^{106}Rh$ (average 1.4 MeV beta) or ^{147}Pm (average 0.06 MeV beta), was around 35 Gy, estimated as dose to crypt cells. The dose to the villus epithelium may be 3 to 4- fold higher. The dose to the crypt epithelium is comparable to the $LD_{50/7}$ after external irradiation (11-15 Gy) when the reduction in effect at the lower dose rate is taken into account.

(129) There are few reports of acute injury to the intestinal mucosa after radionuclide ingestion in humans. Of 22 individuals with extensive internal contamination with $^{137}CsCl$ (>3.1 MBq) in the Goiania accident in Brazil, 8 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 doses estimated between 4 and 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.

(130) 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 spondilitis 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

(131) 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 post-radiation 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 total body irradiation 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

(132) The male genital system consists of three groups of organs: gonads (testicles); sperm storing and ejaculation organs (epididymis, deferent duct, ejaculatory duct); 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 about 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; meiotic maturation of spermatocytes to yield round spermatids; and differentiation of spermatids into mature spermatozoa, known as spermiogenesis (Figure 2.2).

(133) 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 (Figure 2.3). Fallopian tubes capture the ovum during ovulation and ensure its passage into the uterine cavity. The development of the embryo and foetus takes place in the uterus. The walls of the fallopian tubes and the uterus are composed of 3 membranes: the mucous membrane lined with a single layer of columnar epithelium, the muscular and serous membranes. The mucous membrane of the vagina is lined with multi-layer non-keratinising epithelium. The structure of mammary glands changes, depending on age and phase of the menstrual cycle.

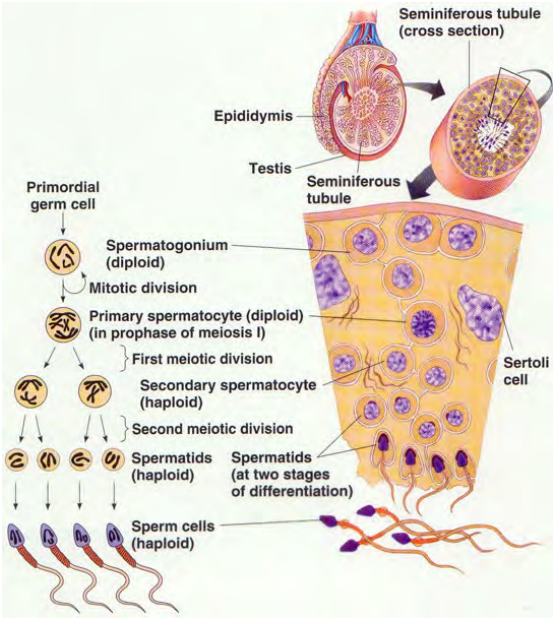

Fig. 2.2. Diagrammatic representation of human spermatogenesis.
http://iceteazegeg.files.wordpress.com/2009/02/spermatogenesis.jpg

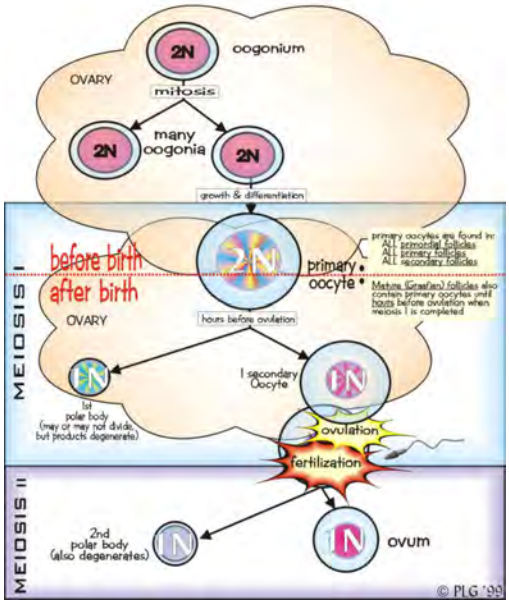

Fig. 2.3. Diagrammatic representation of human oogenesis.
http://science.tjc.edu/images/reproduction/oogenesis.jpg

(134) 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 et al., 1989a, 1989b). The effects of chronic irradiation on the reproductive and sexual functions of human gonads have been studied in radiologists, nuclear workers, persons 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

(135) 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 (Centola et al., 1994; Clifton and Bremner 1983; Rowley et al., 1974; Speiser et al., 1973). The only known example of detailed radiosensitivity/time-course measurements for human spermatogenesis is shown in Figure 2.4.

(136) 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 oligoozospermia, 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 doses (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 4 Gy (Centola et al., 1994; Speiser et al., 1973).

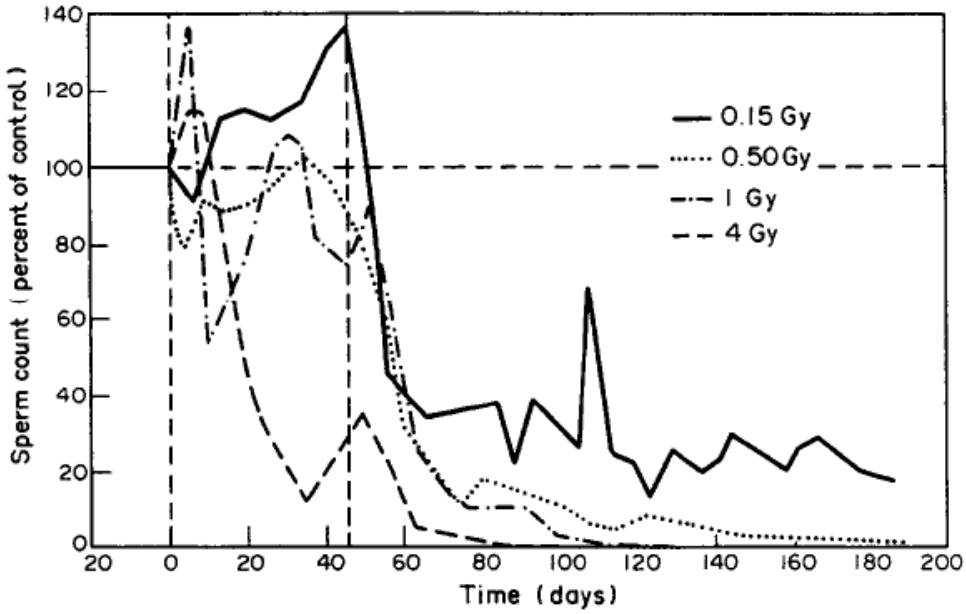

Fig. 2.4. Time course of sperm counts in normal men following high-intensity exposure of the testes to various doses of 190 kVp x-rays (Heller 1967; ICRP, 1984)

(137) Leydig cells are more resistant to damage from radiotherapy than the germinal epithelium. Susceptibility to radiation-induced Leydig cell damage appears to be inversely related to age, or sexual maturation, with greater damage following smaller doses in pre-pubertal 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 greater than 20 Gy is associated with Leydig cell dysfunction in pre-pubertal boys while Leydig cell function is usually preserved up to 30 Gy fractionated dose in sexually mature males (Castillo et al., 1990; Shalet et al., 1989). Pre-pubertal 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, LH (Luteinizing Hormone) levels 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.

(138) 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 GnRH (Gonadotropin Releasing Hormone) 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).

(139) 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; 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 pre-pubertal testis (Kelnar et al., 2002).

2.3.3. Radiation-induced damage to the female reproductive tract

(140) Intact ovarian function demands a critical mass of primordial follicles in an appropriate endocrine mileu. The human ovary has a fixed oocyte pool at birth, which begins an atretic process culminating in menopause 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 total body, 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 LD_{50} of less than 2 Gy (Wallace et al., 1989a, 1989b, 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 long term after TBI (10-15.75 Gy, ~2 Gy per fraction) and in 97% of females treated with fractionated total abdominal irradiation (20-30 Gy, 1-2 Gy per fraction) during childhood (Wallace et al., 1989a). The younger the child at the time of radiotherapy, the larger is the oocyte pool and the later is the onset of a 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).

(141) A number of women may have preservation of ovarian function if the dose to one or both ovaries can be relatively spared, for example 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 abdominal, pelvic or total body 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 (Bath et al., 1999; Critchley et al., 1992). 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 (Chiarelli et al., 2000; Green et al., 2002; Hawkins and Smith, 1989). 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.

(142) Studies in experimental animals have shown a wide range in radiosensitivities of oocytes 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 to acute single doses, but the reverse is found in monkeys and in humans there is no evidence of recovery with dose protraction.

2.3.4. Internal exposures

(143) 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 ~100 cGy), 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 the 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. Risks to the offspring

(144) Concerns have been raised that potentially mutagenic chemotherapy and radiotherapy may cause germ line mutations and pose an increased risk of genetic abnormalities in the children born to survivors of cancer (Boice, Jr. et al., 2003; Winther et al., 2003). The Danish Cancer Registry identified 4,676 survivors of childhood cancer diagnosed between 1943 and 1996 and compared them with a cohort of 6,441 siblings. From this population based study there were 2,630 live offspring born to the survivors and 5,504 live-born offspring of their siblings (Winther et al., 2004). The Danish Cytogenetic Registry was used to determine the occurrence of abnormal karyotypes and of pregnancies terminated following prenatal diagnosis of a chromosomal abnormality. Taking these cases into account, and after exclusion of hereditary cases, there was no

indication of increased risk of chromosomal abnormalities in the offspring. These results are in keeping with other studies of children of survivors of childhood cancer (Byrne et al., 1998). Hawkins explored pregnancy outcome in 2,286 survivors of childhood cancer (1,049 females and 1,237 males) who had been exposed to abdominal irradiation or alkylating agents (Hawkins, 1991). Concurrent with other studies they report an increased risk of miscarriage and low birth weight among the offspring of female survivors who received abdominal irradiation (Chiarelli et al., 2000; Winther et al., 2003). The study did not show an association of exposure to potentially germ cell mutagenic therapy and sex ratio or occurrence of serious congenital abnormalities in the offspring of male or female survivors.

(145) A number of studies have explored the genetic effects of ionising irradiation. The most comprehensive epidemiological study is that of the survivors of the Japanese atomic bombs and their children; this did not show any evidence for inherited defects attributable to parental irradiation (Fujiwara et al., 2008; UNSCEAR, 2001). Further reassurance (Boice et al., 2003) was provided in a large international study in the United States and Denmark involving a cohort of almost 25,000 childhood cancer survivors who subsequently gave birth to or fathered children. In the United States series, congenital abnormalities were reported in 157 of the 4,214 (3.7%) childhood cancer survivors, compared with 95 (4.1%) of the 2339 children of sibling controls. Similar findings were reported in the Denmark series. In female participants in the Childhood Cancer Survivor Study (CCSS), those who received a hypothalamic/pituitary radiation dose > 30 Gy in 2 Gy fractions or an ovarian/uterine radiation dose greater than 5 Gy were found less likely to have ever been pregnant (Green et al., 2009). In males, the hazard ratio for siring a pregnancy was decreased by radiation therapy of more than 7.5 Gy to the testes (Green et al., 2010). These studies indicate some effects of high-dose cancer radiotherapies on fertility in the F1 generation.

(146) It has been suggested that radiotherapy and chemotherapy may induce mutagenic damage to the germ cells and that recessive lethal mutations induced in X chromosome may cause an altered sex ratio in the offspring: e.g., decreased male-to-female ratio in the offspring of female survivors, since male offspring carry only one X chromosome derived from the mother. This theory was postulated following studies in Drosophila, and a large-scale study was subsequently conducted in the offspring of the atomic bombing survivors in Hiroshima and Nagasaki. The results, however, did not indicate any differential effect (Jablon and Kato 1971). Later it was found that in mammalian females one of the two X chromosomes is inactivated at some early stage of embryogenesis (Lyonisation) whereas in fruit flies both X chromosomes are active all through the developmental stages. Thus, in female mammals, there is no guarantee that the heterozygous individuals are fully protected from the effect of X-chromosomal recessive lethal mutations. Further, the fraction of X chromosome to the total genome is quite large (~20%) in fruit flies while it is much smaller (less than 2%) in humans, which makes the detection probability of the effect much smaller if any. Thus, it is not surprising that similar negative results were observed in a number of studies of cancer survivors (Critchley and Wallace, 2005).

(147) Advances in techniques of assisted reproduction, especially intracytoplasmic sperm injection (ICSI), have provided a treatment option to

enable men with oligozoospermia to achieve fatherhood (Aboulghar et al., 1997). Concerns have been raised about the safety of ICSI, particularly relating to the possibility that spermatozoa from men with impaired spermatogenesis may carry abnormal genetic information as a consequence of potentially mutagenic cancer therapy (Irvine et al., 2000). Although the best available data on the health of offspring following ICSI are broadly reassuring, there are no data on the health of offspring where the man's deficit in semen quality is a consequence of potentially mutagenic treatment. Thomson and colleagues have shown that, although there is evidence for impaired spermatogenesis after treatment for childhood cancer, the sperm produced carries as much healthy DNA as sperm produced by the general population (Thomson et al., 2002).

(148) As with males, there is the theoretical risk that combined exposure to chemotherapeutic agents and irradiation may cause mutations and DNA changes to the oocyte. Animal studies have demonstrated high abortion and malformation rates related to different stages of oocyte maturation at the time of exposure to cancer therapy. This has raised concerns regarding the use of assisted reproduction techniques and embryo cryopreservation in patients previously exposed to cancer therapy. Reassuringly, studies of pregnancy outcome in cancer survivors have not substantiated these concerns (Edgar and Wallace, 2007). There is no increased incidence of chromosomal or congenital abnormalities in offspring born to women exposed to cancer therapy. Cancer survivors are understandably concerned about the development of cancer in their offspring. Multiple studies have explored the incidence of cancer in the offspring of cancer survivors and, excluding known cancer predisposition syndromes, there is minimal or no increased risk of cancer development in the offspring (ICRP, 1999).

(149) Although there is no direct evidence that exposure of parents to radiation leads to excess heritable disease in offspring, there is compelling evidence that radiation causes heritable damage in experimental animals. In view of this, mouse data continue to be used as a prudent basis to estimate genetic risks in humans. The new approach to heritable risks continues to be based on the concept of the doubling dose (DD) for disease-associated mutations, but recoverability of mutations in live births is also allowed for in the estimation of DD. In addition, direct data on spontaneous human mutation rates are used in conjunction with radiation-induced mutation rates derived from mouse studies. The current estimate of genetic risks up to the second generation is about 0.2 % per Gy continuous low-dose-rate exposure over those two generations (ICRP 2008), essentially the same as cited by (UNSCEAR, 2001).

2.3.6 Summary

(150) Certain developmental cell stages in spermatogenesis are very sensitive to irradiation, causing transient infertility after several tens of cGy. However, fertility recovers from surviving stem cells even after doses of 4 Gy or more. The endocrine regulatory system is much more resistant, and injured by only high therapeutic radiation doses. The human oocyte is very sensitive to radiation-induced apoptosis, with an estimated LD_{50} of less than 2 Gy. This is the cause of radiation-induced infertility, which occurs more 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. There is no direct evidence that exposure of parents to radiation leads to excess heritable disease in offspring.

2.4. Skin

2.4.1. Anatomical features and proliferative organisation

(151) The skin is one of the major organs of the body (Figure 2.5). In a standard 70 kg man it provides a covering for the body, with a surface area of about 2 m^2, and it has a weight of 2.1 kg, 3% of the 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 onto 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, it senses the external environment and it 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.

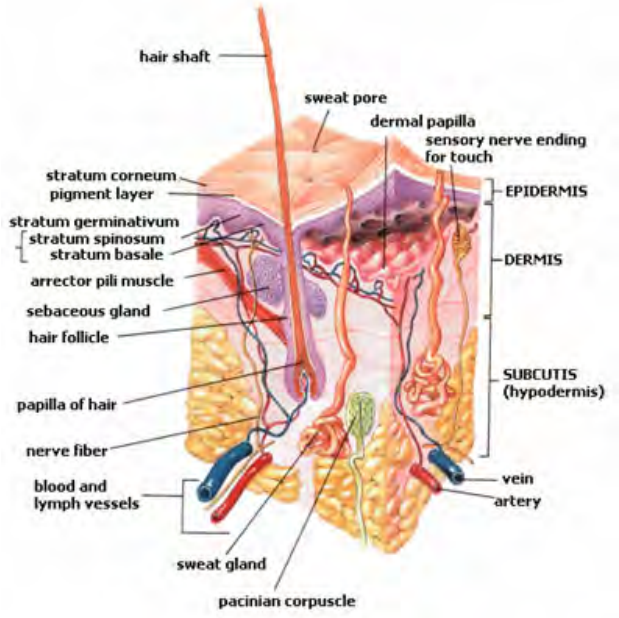

Fig. 2.5. Diagrammatic representation of human skin.
(http://www.web-books.com/eLibrary/Medicine/Physiology/Skin/skin01.jpg)

(152) 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 been described (ICRP, 1991), and they are summarised below: 1) 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. 2) In the viable epidermis, stem cells are restricted to the basal layer, although cell divisions do occur in suprabasal cells. 3) More than 50% of basal cells are to be found at a depth of >200 μm, distributed in the shaft of hair follicles at varying depths within the dermis. 4) The depth of the basal layer in the interfollicular epidermis varies greatly but is between 20 μm -100 μm in most body sites. On the hands the epidermis of the finger tips is thicker, the depth of the basal layer is >160 μm. 5) The products of keratinocytes, such as ETAF (Epidermal cell-derived Thymocyte-Activating Factor) and the Langerhans cells that process antigens, make skin an important component of the immune system. 6) 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. 7) The thickness of the dermis varies with body site but is usually within the range 1.0 mm - 3.0 mm, approximately 10 times the epidermal thickness in a specific site. 8) The upper papillary dermis is very well vascularised. About 90% of the blood flow is associated with temperature regulation. 9) 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

(153) 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 about 8-10 weeks after exposure. This has a bluish tinge and represents dermal ischaemia.

(154) The reaction of the epidermis to radiation exposure is the most extensively documented amongst all tissues. The cells most at 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.

(155) 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.

(156) 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 significantly enlarged 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 (Devalia and Mansfield, 2008; Dormand et al., 2005; Tibbs, 1997). There are examples of radiation effects on wound healing when more than 8 Gy single dose, or its iso-effective fractionated dose, is delivered within a month before or after surgery.

(157) 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 most closely approximates to 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 to 16 weeks (Archambeau et al., 1968; Barabanova and Osanov 1990; Hopewell and Van den Aardweg, 1988). 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 (Joiner and Bentzen 2009; Bentzen and Joiner, 2009). However, during protracted treatments over many weeks, repopulation can influence the effective α/β ratio (see below).

(158) 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.

(159) 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. It should be noted that these skin changes are largely avoided in modern radiotherapy which uses penetrating beams of radiation providing dose sparing in the skin.

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 ED_1 doses.

Effect	Approximate threshold doses (Gy)	Time of onset
Early transient erythema	2	2-24 hours
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 (1st phase)	10	>52 weeks
Telangiectasia	10	>52 weeks
Dermal necrosis (late phase)	>15?	>52 weeks

2.4.3. Dose-effect relationships and threshold doses

(160) It has been a long accepted practice in radiotherapy to reduce the total dose to skin as the treatment area is increased (ICRP, 1991). 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 areas and volume effect relationships for the skin (Von Essen, 1948).

(161) 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 about 69 Gy (Hopewell et al., 1989). These fractionated radiation doses can be used to calculate equivalent acute single doses, by assuming that the underlying cell survival curve of the target cells, the death of which is responsible for the effect, can be described by a linear-quadratic (LQ) equation (see 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 about 17 Gy for the ED_{50} value and about 10.5 Gy for the threshold (ED_1) dose, respectively. For late telangiectasia in

human skin, the ED_{50} for a moderate severity of telangiectasia at 5 years was about 65 Gy for fractionated doses given as 2 Gy per fraction, 5 fractions per week (Turesson and Notter, 1984, 1986), and the threshold dose (ED_1) was about 40 Gy.

(162) 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.

(163) In an experimental study in the pig no field-size effect could be demonstrated when the responses of 4 x 4 cm and 4 x 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 mm to 40 mm diameter, were irradiated with $^{90}Sr/^{90}Y$. The 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 mm^2. The ED_{50} values were found to decline markedly from about 70 Gy for a 5 mm diameter source to about 27 Gy for a $\geq$22.5 mm diameter source. The sparing effect seen for irradiation of very small volumes was attributed to migration of cells from outside the irradiated area. Irradiated areas of 15 mm diameter 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 the ED_{50} for sources of 22.5 mm and 40 mm diameter. The dose-effect curves for the 5, 11 and 15 mm diameter sources had a significantly shallower 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.

(164) The irradiation of skin with a beta-ray emitter of significantly lower energy than $^{90}Sr/^{90}Y$, for example ^{170}Tm (E_{max} 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 the ED_{50}, the ED_{10} and ED_1 doses in pig skin after irradiation with ^{170}Tm sources of 5-19 mm diameter provides major evidence for the presence and importance of viable clonogenic cells within the hair follicle canal.

(165) A comparison of the radiation responses of the skin to $^{90}Sr/^{90}Y$ and ^{170}Tm with that of ^{147}Pm is not entirely meaningful because of the change in the biological response produced by very low energy beta-ray emitters. 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. For irradiations with intermediate and higher energy beta-ray emitters, dermal atrophy and telangiectasia are the cosmetically unacceptable late normal tissue changes that may determine the recommended dose limit in radiological protection. 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 2 mm diameter sources (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.

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

2.4.4. Protraction of exposure

(167) 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 ED_1 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 due mainly 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.

(168) When the exposure is protracted for $\geq$6 weeks, the repopulation of surviving clonogenic cells from within the basal layer will counteract the effects of radiation on the epidermis, leading to increased effective α/β ratios (Hopewell et al., 2003).

(169) For the late dermal changes, where the α/β ratio is about 3 Gy, there is considerable uncertainty about the significance of a time factor, which might be associated with cellular repopulation. Therefore, it is uncertain as to how late dermal effects might be modified by an 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, the ED_1 of about 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.

(170) Simple split-dose studies in the pig, using two equal doses, have suggested that full recovery of the epidermis is completed with a six week interval between doses (Van den Aardweg et al., 1988). However, after daily (5 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 considerably spared due to repopulation and thus the late dermal changes will again predominate.

2.4.5. Summary

(171) The skin demonstrates both early and late reactions after irradiation. Early reactions, from hours to weeks after exposure, include erythema, epilation and desquamation. Late reactions, which occur from months to yeaers 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 do early reactions, except when there are 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 as is the explanation for early-reaction sparing. Regarding radiation protection for protracted or chronic irradiation scenarios, the epidermis will be considerably spared 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

(172) 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. 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, is dispersed. The three separate layers seen in arteries are not well defined in veins. Veins are in general thin-walled with relatively large lumina.

(173) 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 into the ventricles during diastole. The heart valves do not have a blood supply, but they are covered with a specific type of endothelium.

(174) 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 regulation of electrical impulses. The electrical impulse initiates in the sinoatrial node (pacemaker), at the junction between right atrium and superior vena cava, and is propagated to the atrioventricular (AV) node, located between the atria and the ventricles. The distal part of the AV node, the bundle of His, splits into two branches to activate the left and right ventricle, respectively. Norepinephrine and its receptors regulate heart rate and the force of contraction.

(175) 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 mono-nuclear 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 <5 Gy

(176) Circulatory diseases are major causes of disability and mortality, accounting for 30-50% of all deaths in most developed countries. Coronary heart and cerebrovascular diseases are late manifestations of atherosclerotic changes of the arteries and represent the principal causes of cardiovascular disease mortality and morbidity in many populations. These are multi-factorial 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 haemodynamic disturbances and effects of hyperlipidemia may be the most important factors leading to atherosclerotic plaque (Libby, 2002; Lusis, 2000).

(177) Epidemiological data on circulatory disease 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 indications are that 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 an excessively large cardiovascular disease risk associated with low-dose radiation is likely to be a chance occurrence if found in a small cohort, and careful attention to multiple testing issues and the potential for confounding by other risk factors is needed. In large observational studies, associations may still be due to confounding factors or selection bias, especially for simple comparisons of exposed versus unexposed groups.

(178) Concern for an increased risk of cardiovascular disease risk from low-dose radiation first arose from data on several categories of non-cancer diseases from the Japanese atomic bomb survivors, who received single whole-body exposure to a range of doses less than 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 more than thirty potentially informative cohort studies. These included patients irradiated for the treatment of benign diseases with fractionated and localised exposure at less than 5-6 Gy (cumulative dose), people irradiated repeatedly for diagnostic radiation at less than 1 Gy (cumulative dose) and people with chronic occupational exposure, mostly whole-body doses of less than 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; McGale and Darby, 2008). Several other reviews of studies of populations medically, occupationally or environmentally exposed to relatively low-dose radiation have been published recently (Little et al., 2008; Metz-Flamant et al, 2009, 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 statistically significant, possibly resulting from confounding or bias (Little et al., 2010). Further relevant study results, discussed below, are summarised in Table 2.3.

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

Population		**Association between circulatory disease and radiation exposure**	
	Mean dose (range) [b]	**Cardiovascular**	**Cerebrovascular**
Studies reporting a statistically significant positive radiation effect [a]			
Life Span Study A-bomb survivors (Shimizu et al., 2010; Yamada et al., 2004)	Colon: 0.15 Gy (0-4)	Heart disease mortality, 1950-03: ERR/Gy = 0.14 (0.06, 0.23) IHD incidence, 1958–1998 ERR/Gy = 0.05 (-0.05, 0.16)	Cerebrovascular mortality, 1950-03 ERR/Gy = 0.09 (95% CI 0.01, 0.17) Stroke incidence, 1958–1998 ERR/Gy = 0.07 (-0.08, 0.24)
Radiologic technologists, USA (Hauptmann et al, 2003)	Heart: 0.01 Gy (0-0.46)	RR =1.22 (first worked <1940); 1.00 (1940-); 0.98 (1950-); 1.00 (1960+)	RR = 2.40 (first worked <1940); 1.54 (1940-); 0.90 (1950-); 1.00 (1960+)
Patients irradiated	Heart: 1.3 Gy (0-7.6);	IHD mortality:	RR = 1.36 (lowest quartile);

For peptic ulcer, USA (Carr et al, 2005)	Carotid: quartile mean, range, 0.1-0.24 Gy	RR=1.00 (0 Gy); 1.00 (0.1-1.9 Gy); 1.23 (2-2.5 Gy); 1.54 (2.6-3 Gy); 1.54 (3.1-7.6 Gy) ERR/Gy = 0.10 (-0.12, 0.33)	0.99; 0.98; 0.82 (highest category)
Chernobyl accident emergency workers, Russia (Ivanov et al., 2006)	0.109 Gy	IHD morbidity: ERR/Gy = 0.41 (0.05, 0.78)	Cerebrovascular morbidity : ERR/Gy = 0.45 (0.11, 0.80)
British Nuclear Fuels workers, UK (McGeogheagan et al., 2008)	0.53 Sv (99th %, 0.589)	IHD mortality: ERR/Sv = 0.70 (90% CI 0.33, 1.11)	Cerebrovascular motality: ERR/Sv = 0.43 (90% CI – 0.10, 1.12)
Radiologists, USA	Radiologists dying, 1930-54: 8-20 Sv lifetime	SMR (arteriosclerotic heart disease) = 1.03 (radiologists, 1920-39); 1.15 (1940-69)	
Mayak, Russian Federation (Azizova et al, 2010a,b)	External γ: 0.91 Gy (males); 0.65 Gy (females) α Pu: 0.40 Gy (males); 0.81 Gy (females)	IHD, external γ dose ERR/Gy Incidence: = 0.11 (0.05, 0.17) Mortality: = 0.07 (-0.02, 0.15)	Cerebrovascular disease, external γ dose ERR/Gy Incidence: 0.46 (0.36, 0.57) Mortality: -0.02 (-0.12, 0.07)
Studies not reporting a statistically significant positive radiation effect			
Tuberculosis patients USA (Davis et al, 1989)	0.84 Gy (lung)	Mortality from all circulatory diseases: ERR/Gy = -0.11 (-0.20, -0.01)	
Radiologists, UK	Lifetime 20 Sv (radiologists 1897-1920: 3.8 (1921-35); 1.25 (1936-54); 0.1 ; (1955-79)-	RR compared to other medical practitioners (all circulatory disease) =1.30 (radiologists registered 1897-1920); 1.15 (1920-35); 0.84 (1936-54); 0.69 (1955-79)	
Patients with ankylosing spondylitis (Darby et al, 1987; 2005)	Heart: 2.49 Gy (0.0-17.28) Brain: 0.14 Gy (0.0-4.80)	Mortality from circulatory disease, excluding stroke: RR = 0.97 (exposed vs. unexposed), ns ERR/Gy = -0.01 (-0.12, 0.13)	Stroke mortality: ERR/Gy = -2.43 (-4.29, 0.71)
IARC 15-country nuclear workers (Vrijheid et al, 2007)	Cumulative recorded: 0.0207 Sv (0->0.5 Sv)	Circulatory disease mortality: ERR/Sv = 0.09 (-0.43, 0.70) IHD mortality: ERR = -0.01 (-0.59, 0.69)	Cerebrovascular mortality: ERR/Sv = 0.88 (-0.67, 3.16).
National Registry for Radiation Workers, UK (Muirhead et al, 2009)	0.025 Sv	Circulatory disease mortality: ERR/Sv = 0.25 (-0.01, 0.54) IHD: ERR/Sv = 0.26 (-0.05, 0.61)	Cerebrovascular mortality: ERR/Sv = 0.16 (-0.42, 0.91)
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 (-0.7, 0.009)	Cerebrovascular, external γ dose: ERR/Sv = 0.09 (-0.6, 0.8)

IHD = ischaemic heart disease

a: Confidence intervals, in parentheses, are 95%, except where stated otherwise.

b: 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.

Atomic-bomb survivors

(179) Mortality data from the Life Span Study (LSS) of the Japanese atomic bomb survivors provide evidence of a dose response for mortality from heart

diseases, cerebrovascular disease, and other non-cancer diseases (respiratory and digestive diseases) (Preston et al., 2003; Shimizu et al., 1999). About 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 LSS was based on follow-up over the period 1950-2003 (Shimizu et al, 2010) (see Figure 2.6).

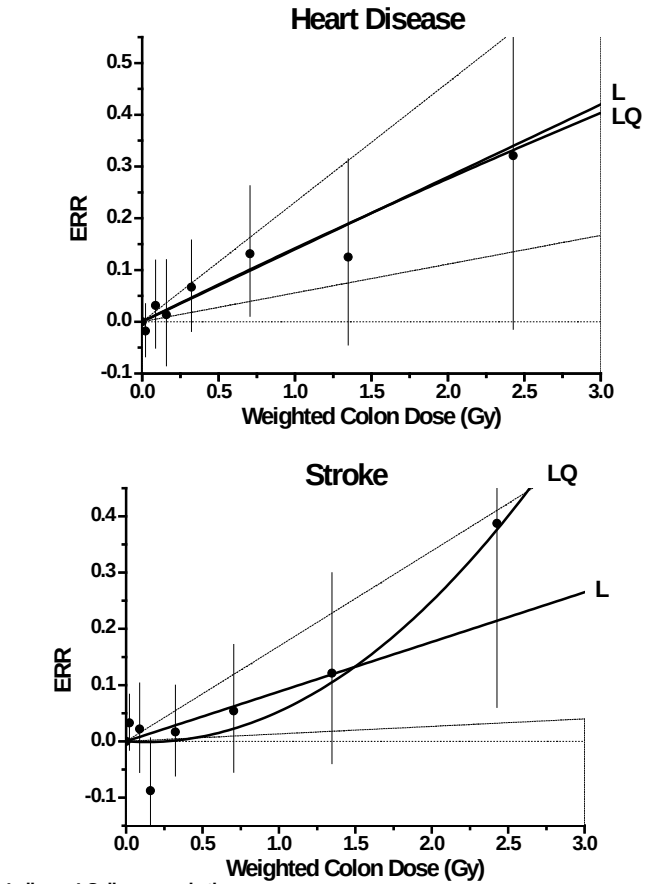

Fig. 2.6. Radiation dose-response, Excess Relative Risk (ERR) for heart disease and cerebrovascular disease mortality, showing the linear (L) and linear-quadratic functions (LQ). Weighted colon dose in Gy is the sum of gamma dose estimate and 10 times neutron dose estimate (from Shimizu et al., 2010).

(180) Although Shimizu et al. (2010) referred to "stroke" in their analyses of ICD9 430-438, "cerebrovascular disease" is referred to here because stroke is usually defined as a subset of these ICD codes. For cerebrovascular disease (ICD 9th codes: 430-438), there were about 9,600 deaths and the estimated excess relative risk per gray (ERR/Gy) was 9% (95% CI: 1 to 17%, p=0.02) based on a linear dose-response model. However, indications of possible upward curvature suggested there was relatively little risk at low doses. There were about 8,400 deaths from heart disease as a whole (ICD 9th codes: 390-398, 402, 404, 410-429). This is lower than the value that would be expected for population 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 to 23%, p<0.001); a linear model provided the best fit to these data. However, the dose-response over the restricted dose range of 0 to 0.5 Gy was not statistically significant,

whereas the corresponding dose-response over 0-1 Gy was statistically 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 sub-types of heart disease on death certificate diagnoses such that limited meaning could be attached to the results of the analyses performed of various sub-types of cardiovascular disease. That said, analyses specific to various types of heart disease found that the evidence for a association was greatest for hypertensive heart disease, rheumatic heart disease and heart failure. However, 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 0.00, 95% CI: -0.15 to 0.18).

(181) 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 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.

(182) Analysis of mortality over 1950-2003 in the LSS showed no statistically 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 age 60 than after, especially among men, but the interpretation of this sub-group analysis is limited. There was also a nonsignificant indication of an age at exposure effect for cerebrovascular disease (ERR/Gy of 0.36, 0.09, 0.15 and 0.05 for ages <10, 10, 20-, 40+ at exposure, respectively).

(183) A significant dose response was also found in a study of 288 incident cases of myocardial infarction, in the clinical (Adult Health Study) subset of the LSS cohort (Kodama et al., 1996). The relative risk 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 heart disease incidence and prevalence in the Adult Health Study participants (1.05 at 1 Sv, 95% CI: 0.95-1.16). However, there is potential survivor/selection bias involved in prevalence cases.

(184) Clinical laboratory data from the clinical Adult Health Study subset also provide some insight into sub-clinical 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 inflammation markers among the cohort subjects, including C-reactive protein (CRP), IL-6 and sialic acid (Hayashi et al., 2003; Neriishi et al., 2001). Elevated CRP 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 promotion of pre-clinical inflammation.

Medical exposures

(185) Observational studies of populations irradiated for treatment of non-malignant diseases can provide information on the cardiovascular disease risk associated with exposure to fractionated doses at less than 5 Gy. It is necessary, however, to consider the confounding effect of the non-malignant diseases for which radiation treatment was given, and also the reasons that patients were treated with radiation rather than by other means, such as surgery. For example, thyroid disease may predispose to an increased risk of cardiovascular disease because of altered thyroid hormone levels. Women given ovarian irradiation for uterine bleeding or other gynaecological disorders were probably in a hyper-estrogenic status, 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 exposed populations are not included in this review.

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

(187) A significant dose response 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 for coronary heart disease for doses of 1.6 to 3.9 Gy to the entire heart, or from 7 to 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 carotid radiation dose and cerebrovascular disease, but the doses to the carotid artery were only about 10% of those to the heart. The

uneven distribution of radiation doses to the heart (high doses in a small portion and low doses in the remaining part of the organ) complicates the interpretation of these data, especially for low-dose effects.

(188) Repeated radiological diagnostic or intervention procedures may lead to a significant radiation exposure. In 2006, the per capita dose from medical exposure (not including dental or radiotherapy) in the U.S. was approximately 3.0 mSv. These exposures were mostly from CT-scans followed by angiography and vascular interventions.

Occupational exposures

(189) 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 per year and that they may have received annual exposure of 0.1 Sv before the 1950s and about 0.05 Sv in the early 1950s; the average lifetime dose was estimated to be 20 Sv in the radiologists who were registered between 1897 and 1920, 3.8 Sv in 1921-1935 radiologists, 1.25 Sv in 1936-1954 radiologists and 0.1 Sv in those registered between 1955 and 1979 (Berrington et al., 2001; Braestrup, 1957; Smith and Doll, 1981). For US radiologists dying between 1930 and 1954, estimated lifetime (40-year) cumulative doses range from 8 to 20 Sv (BEIR I, 1972). These dose estimates, naturally very crude, give some idea of the extent of exposure among the early radiologists in general, but not individual variation. Studies of the UK and US radiologists provide conflicting results regarding circulatory or heart disease mortality risk among the early radiologists compared with other medical professions (Berrington et al., 2001; Matanoski et al., 1984). Individual dose estimates are lacking in these studies therefore quantitative risk estimates are not possible. Among US radiologic 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.

(190) Analyses of studies of nuclear workers can provide direct estimates of risks at the lowest dose range, less than 0.5 Gy, based on 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 for 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 (250 mSv or more) were excluded from this analysis (Vrijheid et al., 2007). The ERR/Sv for circulatory disease (including ischaemic heart disease), adjusted for socioeconomic status was 0.09 (95% CI -0.43 to 0.70) (Vrijheid et al., 2007). 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.

(191) Another pooled analysis involved about 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 over 90% of this cohort), there was a significant dose response (cumulative external dose) for mortality from circulatory disease with an ERR/Sv of 0.65 (90% CI 0.36 to 0.98) and an ERR/Sv of 0.70 (90% CI 0.33 to 1.11) for ischaemic heart disease (McGeoghegan et al., 2008). The ERR/Sv for cerebrovascular disease was also elevated (0.43, 90% CI -0.10 to 1.12), but this was not significant. There was a significant heterogeneity in the dose response among different categories of employment and radiation exposure (internal vs. external), which remained unexplained and prevented the authors from making a causal interpretation.

(192) A subsequent analysis of a larger cohort of about 175,000 radiation workers in the UK, including virtually all of the workers in the study of McGeoghegan et al., 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 to 0.49, 95% CI -0.01 to 0.54) and from ischaemic heart disease in particular (ERR/Sv 0.26, 90% CI 0.00 to 0.55, 95% CI -0.05 to 0.61) (Muirhead et al. 2009). However, the similar dose patterns in circulatory disease and lung cancer mortality suggested some confounding by smoking, but the direction and magnitude of this effect could not be quantified. More generally, the lack of information on confounders, and not knowing the extent to which they may influence the dose response, hamper the assessement of the radiation-related cardiovascular disease risk associated with occupational exposure.

(193) Circulatory disease mortality and incidence have been studied in a cohort of about 12,000 workers at the nuclear plants of 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).

(194) Having adjusted for non-radiation factors, there were statistically significant increasing trends with both total external gamma dose and internal liver dose in IHD incidence among Mayak workers (Azizova et al, 2010a). The trend with internal dose was weaker and not statistically significant after adjusting for external dose, whereas the external dose trend was little changed after adjusting for internal dose. The trend with external dose in IHD mortality was not statistically significant, but was consistent with the corresponding incidence trend. There were also statistically significant increasing trends in the incidence of, but not mortality from, cerebrovascular disease with both total external gamma dose and internal liver dose (Azizova et al, 2010b). Much of the evidence for raised morbidity from IHD and cerebrovascular disease arose for workers with cumulative gamma doses above 1 Gy. Although the dose responses for external radiation and circulatory disease incidence were consistent with linearity (ERR/Gy = 0.11 (95% CI 0.05 to 0.17) for IHD and

0.46 (95% CI 0.36 to 0.57) for cerebrovascular disease), the statistical power to detect non-linearity at gamma doses below 1 Gy was low.

Astronauts and airline crew

(195) 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 International Space Station astronauts showed average effective doses for 6-month missions of 72 mSv (Cucinotta et al., 2008). There are currently no empirical data on radiation-related cardiovascular disease risk 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).

(196) 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 cardiovascular disease risk among airline crew (Blettner et al., 2003; Zeeb et al., 2003).

Accidental exposures

(197) Fourteen years after the Chernobyl accident, the ERR per Gy for ischaemic heart disease was estimated to be 0.41 (95% CI 0.05 to 0.78) per Sv in the Russian cohort of 61,000 emergency workers, with a mean dose of 109 mGy (Ivanov et al., 2006). However, the ERR/Gy was smaller (0.10), and not significantly elevated, in a sub-cohort 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 162 mGy. The ERR/Gy for cerebrovascular disease was significantly elevated in the entire cohort (0.45) and in the sub-cohort (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 exposure doses

Cardiac toxicity- randomised trials and epidemiological studies

(198) Radiation-induced heart disease in cancer survivors includes a wide spectrum of cardiac pathologies, such as coronary artery disease, myocardial dysfunction and pericardial disease. Valvular heart disease and 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.

(199) Cardiac effects have been most extensively investigated in long-term follow up studies of irradiated breast cancer and Hodgkin's lymphoma patients, although there are also some data for other diseases. Epidemiological studies on survivors of Hodgkin's lymphoma show strongly elevated risks for cardiac

deaths, with RRs in the range of 2 to >7, leading to 15 to 40 extra cardiac deaths per 10,000 persons per 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 (Adams et al., 2003; Aleman et al., 2003; Boivin et al., 1992; Hancock et al., 1993; Swerdlow et al., 2007). Radiation causes both increased mortality (mainly fatal myocardial infarction) and increased morbidity. For instance, 3 to 5-fold increased standardised incidence ratios (SIR) of various heart diseases were observed in >1,400 patients treated for Hodgkin's lymphoma before the age of 41 years, relative to the general population, even after a follow-up of more than 20 years (Aleman et al., 2007). This study demonstrated that the risk was significantly greater for patients irradiated at young age; SIR for myocardial infarction 2.6 (95% CI 1.6 to 4.0) for patients irradiated at age 36 to 40, compared with SIR 5.4 (95% CI 2.4 to 10.3) for those irradiated at age <20 years. 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, valvular and conduction defects, are very common, even in asymptomatic Hodgkin's lymphoma survivors (Adams et al., 2004). Hodgkin's lymphoma patients also have a significantly higher risk (SIR 8.4, 95% CI 3.2 to 13.7) of requiring valve surgery or revascularisation procedures 15 to 20 years after radiotherapy (Hull et al., 2003).

(200) 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 RR are lower than for Hodgkin's lymphoma patients, the very large number of women irradiated for breast cancer make this a significant health concern. The large number of randomised controlled trials carried out on breast cancer patients 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 versus no radiotherapy, with the same surgery, and from 9,300 women in 17 trials of radiotherapy versus 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; 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 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) versus right-sided (RR 1.18) breast cancer (estimated mean cardiac doses 12 Gy 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 to 1.63, SE 0.19 at >15 years).

(201) 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 heart disease rates in populations of women with left-sided and right-sided breast cancer. Data from the SEER (surveillance, epidemiology and end-results cancer registries) cancer registries provide further convincing evidence of increased risk of myocardial infarction in women irradiated for breast cancer (Darby et al., 2005; Paszat et al., 1998). 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 versus right-sided disease (RR 1.2 overall and 1.4 at >10 years).

(202) 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 breast cancer patients 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 hazard ratios (HR) 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).

(203) 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 (Zagers et al., 2004) following infra-diaphragmatic radiotherapy when compared with surveillance only. Other studies did not find a significant increase in the incidence of cardiovascular disease after sub-diaphragmatic irradiation, although mediastinal irradiation was a risk factor (Van den Belt-Dusebout et al., 2006; 2007).

(204) 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. anthracylines 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 (Kremer et al., 2001; Steinherz 1997). A recent 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 risk of myocardial infarction and angina were not further increased by anthracyclines.

(205) The risk of cardiovascular diseases might also be increased through indirect effects of radiotherapy e.g. 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, hypercholesterolemia, overweight and smoking probably also contribute to the risk of cardiovascular diseases in patients treated with radiotherapy (Bowers et al., 2005; Glanzmann et al., 1994; Hooning et al., 2007; Harris et al., 2006). Whether the cardiovascular risk factor profile in patients treated for malignancies differs from that of the general population is unknown.

(206) Cardiovascular toxicity following radiotherapy and/or chemotherapy is expected to change in the future. On the 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 like anthracyclines, taxanes and newer medicines like trastuzumab may influence the incidence of cardiovascular problems. In addition, intensity modulated radiotherapy (IMRT) of lower stage malignancies, for instance 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

(207) In a slow turnover tissue like 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 to 4 Gy from animal studies (Gillette et al., 1989; McChesney et al., 1988; Schultz-Hector, 1992). This indicates that large doses per fraction will be relatively more damaging to the heart than low doses per fraction and, indeed, increased complication rates were reported for Hodgkin's lymphoma patients treated with 3 x 3.3 Gy per week, compared with patients treated with 4 x 2.5 Gy per week to the same total dose (Cosset et al., 1988).

(208) 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 post-operative breast cancer, for example, the breast is generally treated to 50 Gy in 2 Gy fractions and the tumour bed is frequently irradiated to 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 have estimated that, after correction for fractionation effects using the linear-quadratic model and an assumed α/β ratio of 1-3 Gy, equivalent single doses averaged over the entire heart are typically 1 to 2 Gy (Schultz-Hector and Trott, 2007). 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 A-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 is therefore seems prudent to assess dose response relationships for cardiac damage separately for different exposed populations.

(209) 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 Hodgkin's lymphoma patients 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 risks 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 1/3, 2/3, and the whole heart irradiation using 2 Gy per fraction (Emami et al., 1991). However, lower mean heart doses of 26 to 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 was also found to be predictive, with 13% and 73% pericarditis for V_{30} of < 46% versus > 46% (Wei et al., 2008).

(210) Dose volume effects for long-term cardiac mortality have been analysed for Hodgkin's lymphoma and breast cancer patients (summarised in Gagliardi et al., 2001; Gagliardi et al., 2010). These analyses show a smaller dependence for risk of damage on volume irradiated than for pericarditis. The predicted NTCP varied from about 7% to 20% for one third to total volume exposed to 40 Gy (total fractionated dose). NTCP models further predicted that if <10% of the heart is exposed to 25 Gy (fractionated) then the probability of cardiac mortality at 15 years is <1% (Gagliardi et al., 2010) (see also Appendix B). 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 (Girinsky et al., 2000; Levitt 1992; Marks et al., 2005; Rutqvist et al., 1992).

(211) Several studies using functional imaging have shown myocardial perfusion changes at relatively short times after irradiation (< 5 years) (Gyenes et al., 1996; Marks et al., 2005; Seddon et al., 2002). 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% versus 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 yet been demonstrated.

(212) There is currently a major effort to use virtual simulation and computed tomography (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 about 25% of the volume in older studies (Gaya and Ashford 2005).

Radiation damage in major arteries

(213) Head and neck cancer patients, 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 head and neck cancer patients was 21-times that expected in the general population (Muzaffar et al., 2000). Studies comparing left versus 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).

(214) 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).

(215) Significantly increased risks of stroke have been described in adult patients treated with radiotherapy for head and neck cancer (60-70 Gy), with RR in the range 2-9, depending on follow-up and age at irradiation, (Dorresteijn et al., 2002; Haynes et al., 2002; Scott et al., 2009). For example, the study of Dorresteijn showed that the RR of stroke was 3.7 (95% CI 1.3-8.0) for a follow up of <10 years, compared with 10.1 (95% CI 4.4-20.0) for follow up >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 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 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 Hodgkin’s lymphoma patients 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 to 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 TIA (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 at the time of treatment; this younger group had higher risks of cerebrovascular damage than the total cohort (SIR 3.8, 95% CI 1.6-7.4, for stroke and 7.6, 95% CI 2.4-17, for TIA). A systematic review including 6908 patients from institutional series or cohort analyses comparing the frequency of cerebrovascular events in irradiated versus 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).

(216) There is much less agreement on whether radiation is a significant risk factor for stroke in breast cancer patients. 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 to 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 of stroke (OR 1.3, 95% CI 0.8-2.2) compared to no radiotherapy, although a pooled analysis of radiotherapy to internal mammary chain and supraclavicular nodes, compared to no radiotherapy or radiotherapy excluding internal mammary chain and supraclavicular nodes, showed a significant increase (OR 1.8; 95% CI 1.1-2.8). By contrast, another large cohort study (>4,000 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 increase risk associated with hormonal therapy (Hooning et al., 2006). The EBCTCG collaborative meta-analysis of patient data from 46 randmised trials also showed that the risk of stroke was not significantly increased by radiotherapy (Clark 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

(217) The treatment of coronary artery disease has changed over the last decades, from medical treatment, to percutaneous transluminal coronary angioplasty (PTCA), 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 PTCA and stenting (Sindermann et al., 2004). Radiation potentially offers an effective means of dealing with that response. Trials of intra-luminal irradiation, either using a radioisotopic stent or intra-luminal brachytherapy, revealed impressive results, with up to 4-fold decreases in restenosis reported after delivering a single dose of 10 Gy 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.

(218) The situation was different for the treatment of newly diagnosed stenosis with radioactive stents or intra-luminal 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 EC 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).

(219) 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 in patients for a variety of arteries, such as femoral and coronary arteries. A recent 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 to bare metal stent alone. Drug-eluting stents appeared to provide similar results to that of 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

(220) All structures of the heart and major arteries can be damaged by ionising radiation. Damage to the vascular endothelium of large arteries leads to accelerated atherosclerosis and an increased risk of vascular stenosis and thromboembolism (Adams and Lipshultz, 2005; Stewart et al., 1995; Veinot and Edwards, 1996). Early inflammatory changes in the endothelial cells of irradiated large vessels lead to monocyte adhesion and trans-migration into the subendothelial space. In the presence of elevated cholesterol levels these invading monocytes transform into activated macrophages, which ingest lipids and form fatty streaks in the intima, thereby initiating and accelerating the process of atherosclerosis. Proliferation of myofibroblasts is then stimulated by the production of inflammatory cytokines, resulting in a reduction of the arterial lumen (Stewart et al., 2006; Tribble et al., 1999; Vos et al., 1983). Experimental studies have shown that radiation predisposes to the formation of macrophage rich, unstable plaque, rather than stable collagenous plaque (Pakala et al., 2003; Stewart et al., 2006). Such lesions are more likely to rupture and cause a fatal heart attack or stroke.

(221) Radiation-induced damage to the myocardium is primarily caused by damage to the microvasculature, leading to focal interstitial fibrosis. Diffuse fibrosis, with or without calcifications, may also be observed without signs of post inflammatory changes or thrombi. 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. 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 is unclear.

(222) After high doses to the heart (> 40 Gy fractionated), acute pericarditis (protein rich exudate in the pericardial sac) is likely to develop within 6

months. This may resolve in time but it can also progress to fibrin deposition, leading to a thickened pericardial sac and chronic constrictive pericarditis.

(223) 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 et al. 2001; Fajardo and Stewart, 1970; Lauk, 1987; Schultz-Hector, 1992). Although the remaining capillary endothelial cells respond to damage by 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.

(224) Myocardial degeneration, seen from about 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). By 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.

(225) 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 at 6 months to 5 years after radiotherapy (Gyenes et al., 1996; Marks et al., 2005; Seddon et al., 2002). 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.

2.5.5. Summary

(226) Data from the LSS cohort of Japanese atomic bomb survivors show an excess risk of mortality from circulatory disease. The excess relative risk based on the linear model is estimated to be 0.14 per Gy (95% CI: 0.06 to 0.23) for heart disease overall (ICD 9th revision codes: 390-398, 402, 404, 410-429) and 0.09 (95% CI: 0.01 to 0.17) for cerebrovascular disease (ICD9 codes: 430-438) for the period of 1950-2003. The shape of the dose response is consistent with linear, linear-quadratic 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. However, there is considerable uncertainty about the shape of the dose response at doses below 0.5 Gy. Although there was substantial misclassification of sub-types of heart disease on death certificate diagnoses, the evidence for an association with radiation is greatest for hypertensive heart disease, rheumatic heart disease and

heart failure, rather than for ischaemic heart disease, which has been the focus of investigation in other studies of cardiovascular disease.

(227) 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 and to other unknown reasons.

(228) 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 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.

(229) 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

(230) 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 et al., 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). Because of the unique anatomy of the lens, disruption of the integrity of the epithelial cell layer is likely to lead to cataract (Cogan at al., 1952; von Sallmann, 1957; Worgul et al., 1989).

(231) 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 (GZ). The mitotic index of cells more anterior to this region, in the central zone (CZ), is negligible (von Sallman et al., 1962; McAvoy, 1978), but these CZ cells play an important role in maintaining lens metabolism and homeostasis (Kuck, 1970). Following terminal cell division, GZ cells 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 hour 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 hours. Qualitatively, the same phenomena are true for all mammalian lenses. As aging proceeds, the rate of fibre cell formation decreases but never stops (Harding et al., 1971).

2.6.2. Cataract formation

Background

(232) The principal pathology of the lens is its opacification, termed cataract in its advanced stages (van Heynigen, 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 foetal 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).

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

(234) 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 0.2-0.5 Gy, whereas other ocular pathologies in other tissues occur after acute or fractionated exposures of between 5 and 20 Gy.

(235) Ocular radiation exposure results in characteristic lens changes including cataract (Cogan and Donaldson, 1951; ICRP 14, 1969; Kleiman, 2007; Merriam et al., 1983; NCRP 132, 2000). 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.

(236) In spite of the well documented history of radiation-induced cataract (Bateman, 1971; Bellows, 1944; Ham, 1953; Koch and Hockwin, 1980; Lerman, 1962; Merriam et al., 1972; Radnot, 1969; Worgul and Rothstein, 1977), 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, 1991, 2007; NCRP, 2000). The ICRP has published threshold values for detectable opacities of 5

Sv for chronic and 0.5-2.0 Sv for acute exposures (ICRP, 2007). The ICRP and the U.S. National Council on Radiation Protection and Measurements (NCRP) have reported threshold values for visually disabling cataracts of 2-10 Sv for single brief exposures and >8 Sv for protracted exposures (ICRP, 2007; NCRP, 1989). Nevertheless, in its latest recommendations, ICRP (2007) states 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*."

(237) 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 CAT scans (Klein et al., 1993) or radiotherapy (Hall et al., 1999; Wilde and Sjostrand, 1997), in 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., 2001, Hsieh et al., 2010), victims of the Chernobyl nuclear accident (Day et al., 1995; Worgul et al., 2007), radiologic technologists (Chodick et al., 2008), interventional radiologists (Junk et al., 2004) and interventional cardiologists (Kleiman et al., 2009, Vano et al., 2010). These human epidemiological studies, as well as recent work with experimental radiation cataract in animals, suggest that cataract 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 or astronauts.

(238) Not all recent studies, however, support the observation of a lower threshold for radiation cataract. 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 below 10 cGy and a threshold between 10-50 cGy can not be excluded. Similarly, Chmelevsky and coworkers (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 below 2 Gy was not associated with cataract development.

(239) The concept of a dose threshold is critical not only to risk assessment but also to theories regarding the pathological mechanisms of radiation cataract. It should be noted that early studies of radiation cataract generally had short follow-up periods, failed to take into account 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., 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 exam 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 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 cataract. Lastly, it should be recognised that the purpose of radiation protection is to prevent tissue damaging effects of clinical significance and 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 roughly equalised (NCRP, 1989, 1993, 2000).

Examination and quantitation of lens changes

(240) 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.

(241) 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, Worgul et al., 2007, Kleiman, 2007, Vano, 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 ten 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 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. Lesser 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).

(242) Another system, Focal Lens Defects (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., 1994; Chen et al., 2001).

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

(244) A commonly used approach for quantitating cataract of various etiologies is based on the Lens Opacity Classification System versions II (Chylack et al., 1989) or III (Chylack et al., 1993). In the third revision, LOCS III provides a simple and accurate means to subjectively grade cataract type and severity by comparing an individual’s lens image to a set of standard

photographs that illustrate differing severity of nuclear, cortical and posterior subcapsular 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 the 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.

(245) A typical Scheimpflug image of a human radiation cataract is shown in Figure 2.6 (left) and a typical retroillumination image of minor posterior lens changes, including dots and vacuoles, is shown in Figure 2.7 (right).

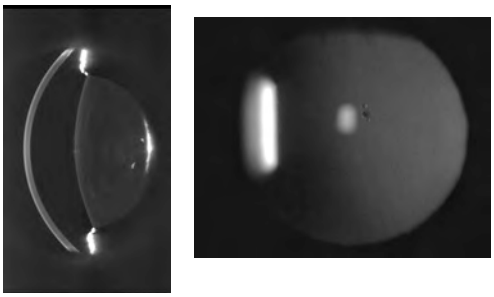

Fig. 2.7. Left picture: Typical Scheimpflug slit lamp biomicroscopic image of a human posterior subscapsular radiation cataract. Right picture: Retroillumination image of an early posterior lens change associated with radiation exposure.

(246) The clinico-histopathological 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 posterior subcapsular region of the lens. Human cataract prevalence is generally low below 60 years of age and PSC represent only a small fraction of cataract types at any age (EDPRG, 2004; Varma and Torres, 2004; Klein et al., 2008). Only a modestly-increased age-related risk for PSC has been reported (e.g., Varma and Torres, 2004). While other environmental insults may also result in psc formation, for example corticosteroid treatment (Urban and Cotlier, 2006), chronic uveitis (Worgul and Merriam, 1981), diabetes (Jeganathan et al., 2008) or galactosemia (Beigi et al., 1993), radiation exposure is generally associated with this type of lens opacification (Cogan et al., 1952; Merriam and Worgul, 1983; Worgul et al., 1976). Variability in sunlight or uv light exposure is unlikely to be a contributory factor as such cataracts are generally associated with superficial cortical opacification (Robman and Taylor, 2005). 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).

(247) 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 and Szechter, 1973, 1975; Merriam et al., 1972). During the period of rapid lens growth in infancy, the lens epithelium appears most sensitive to ionising radiation. Once past adolescence, experimental animal work suggests that for doses below 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 cataract is inversely related to dose and depends on the rate at which damaged lens epithelial cells divide, aberrantly differentiate and migrate to the posterior pole (Worgul and Rothstein, 1975).

Dose response and cataract threshold

(248) The ocular-radiation protection standards, formulated by the NCRP and the 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 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 and 8 Gy for chronic exposures. Several recent lines of evidence from experimental and epidemiologic studies have, however, suggested these values may be too high and that radiation cataract may be even 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.

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

(250) 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) (Figure 2.8). Di Paola 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, in his NASCA study of astronauts, used a similar approach to score PSC “centres” and suggest a relationship between galactice cosmic radiation exposure and PSC size (Chylack et al., 2009, Blakely et al., 2010). Using this approach, if a minimum number of damaged cells were required before a lens opacity were clinically observed, that would suggest a requirement for a threshold radiation dose and therefore radiation cataract could be classified as a “deterministic”-type response (see dashed line in Figure 2.8).

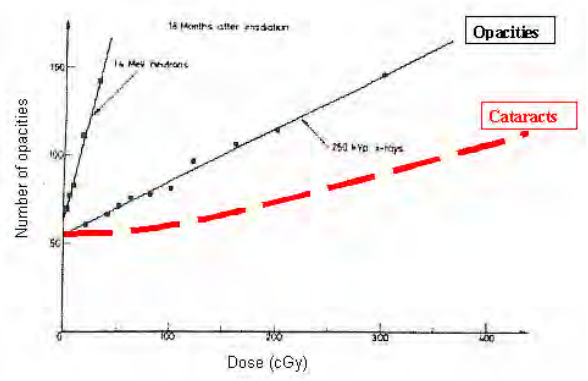

Fig. 2.8. Number of opacities in the murine lens as a function of 250 kVp X rays or 14 MeV neutrons, taken from Di Paola, et al., (1978). The dashed line that has been added here, represents the shape of a curve expected if cataract results from the accumulated damage to many lens cells.

(251) On the other hand, radiation cataract formation could be explained by initial damage to single lens epithelial cells, which upon cell division and differentiation result 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 demonstrate that radiation cataract 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 cataract could 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 a later section.

2.6.3. Epidemiological studies

(252) 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 reduce the uncertainty surrounding the concept of a dose threshold for radiation cataract. Such studies may help determine whether current dose limits are appropriate and/or provide insights into the relevance of radiation cataract to overall human health and radiosensitivity (Table 2.4).

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

Table 2.4. Recent human epidemiological studies that support or question a lower or zero threshold model for radiation cataract.

A) Studies supporting a lower or zero threshold	
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, Jr. 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., 2001 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 Vano et al., 2010
B) Studies questioning lower or zero threshold	
Diagnostic procedures	Hourihan et al., 1999
Radiotherapy	Chmelevsky et al., 1988
Nuclear plant workers	Voelz, 1967 Guskova, 1999 Mikruiukova et al., 2004 Okladnikova et al., 2007

A-bomb survivors

(254) A recent report which examined dose response and threshold in atomic bomb survivors who had cataract surgery is of great interest (Neriishi et al., 2007). These findings are the first to document clinically relevant visual disability many years after low dose radiation exposure. The authors reported a statistically significant, dose-response increase in the prevalence of cataract surgery with an OR at 1 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 A-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 over 0.8 Gy.

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

(256) More recently, Minamoto and colleagues (2004) reported examination of 913 individuals from 2000-2002, mostly including persons who were younger than 13 years at the time of the bombings. Slit lamp and retroillumination examinations of individuals 54 to 94 years of age (mean 64.8 yrs) from both Hiroshima and Nagasaki were completed and graded according to the LOCS II methodology. Doses were based on DS86 dosimetry. A significant increase in cortical and posterior subcapsular cataracts was reported with increasing radiation dose adjusted for city, age, gender and smoking.

(257) 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 as 0.6 Gy (90% CI: <0.0, 1.2) for cortical cataract and 0.7 Gy (90% CI: <0.0, 2.8) for PSC (Nakashima et al., 2006). It should be noted, however, that A-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

(258) 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 that received by A-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).

(259) 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 8,607 "Liquidators" responsible for the cleanup of radioactive materials after the accident, used conventional slit-lamp biomicroscopy of carefully selected subjects with well documented low-dose exposures twelve and fourteen years after the accident. Participants, almost exclusively males, averaged 33 years of age at exposure and thus were at low risk for any kind of pre-existing lens opacification. At the first exam, 12 years after exposure and at an average age of 45, a 30% prevalence of pre-cataractous changes was noted with a 20% prevalence for stage I 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 begun to cause pre-cataractous lens changes. Confounding variables, including age, smoking, diabetes, corticosteroid use, and occupational exposure to hazardous chemicals or ultraviolet radiation were included in the analysis.

(260) Stage 1 opacities demonstrated a dose response for both PSC (odds ratio at 1 Gy (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 cataract 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 about 350 mGy and the confidence intervals excluded values greater than 700 mGy. 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 less than 1 Gy.

(261) Knowing that the latent period for radiation cataract is inversely related to dose, continued follow-up of the UACOS cohort offers the opportunity to further refine the presumptive radiation cataract threshold. As the average age of the Liquidators is now only 53 years and 94% received exposures less than 400 mGy, future ocular examinations over the next decades have the potential to provide more precise statistical support for current or future radiation cataract estimated threshold values.

Techa River Studies and other similar installations in the former USSR

(262) 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 cataract have not yet been reported from such studies.

(263) 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 ocular examinations were performed from 1951-1999 among approximately 30,000 individuals exposed to radioactive contamination while living alongside the Techa river system from 1950-1952

(Mikryukova et al., 2004). This study of "visual disturbances" reported a wide range of ocular diagnosis in the subject population and specifically noted that cataract represented the most frequently diagnosed pathology comprising 26% of all cases. An attempt to make some estimates of excess relative risk of all eye disease due to radiation exposure suggested a weak association. Individual risks for cataract or any other specific ophthalmic disorder were not provided.

(264) 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 posterior subcapsular cataract with accompanying visual loss, chronic exposures of the same doses did not result in cataract, visual disturbances or eye pathology of any kind. Specific types of exposure and/or individual cases were not delineated nor were supporting references provided.

(265) One case of occupationally associated radiation cataract was reported among 37 cases of Acute Radiation Syndrome (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 1,828 subjects diagnosed with Chronic Radiation Syndrome (CRS) and who received total cumulative external doses of 0.5-8 Gy γ-radiation (2-3 Gy/year maximum) or combined external γ 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 exams were not provided.

(266) Similarly, 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 cataract was noted only in acutely exposed workers (>4 Gy) (Okladnikova et al., 2007). No specific details were provided.

(267) In contrast, 3 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 6 cases, three of which included individuals with CRS 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 and colleagues (1994), which stated that none of the subjects with CRS in that study had radiation cataracts. It is difficult to compare the two studies without additional information about the study populations.

(268) A general statement concerning the Russian studies may be made that while radiation cataract has been noted in individuals acutely exposed to radiation of various qualities in excess of 2 Gy, none of the published findings suggest that chronic or low-dose exposure is associated with visual disability and/or radiation cataract. It is difficult to reconcile these studies with the

various recent works in the West, other than to say 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 cataract and ultimate diagnosis may be significantly different.

Radium exposures

(269) 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.

(270) 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 relation 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 suggest, based on measurement of axial distance and human lens growth rates, that this region corresponds to lens fiber cells improperly formed some 30-35 years earlier. The authors also suggest the histological appearance of the lens, which includes abnormally differentiated epithelial cells, lends further support to the theory that radiation cataract arises from the improper division and differentiation of irradiated lens epithelial cells.

(271) In comparison to the previous study documenting radiation cataract following brief but chronic external (low-LET) radium exposure, Chmelevsky and colleagues (1988) reported radiation cataract arising in a population therapeutically treated with ^{224}Ra for tuberculosis and anklyosing 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 to 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 of which 25 occurred before age 54; 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 made only in 11 cases, although posterior subcapsular cataracts were documented in the majority of these. 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 compatible with a linear dependence on dose only beyond an initial threshold exposure. There was little correlation between dosage and age at diagnosis beyond age 60. The authors concluded that their data were most compatible with a deterministic view of radiation cataract with a threshold on the order of 0.5 MBq/kg body weight. This conclusion is undermined, however, by the lack of classification of cataract 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

(272) 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 29-86 mSv. A small but statistically significant increase in the incidence of sub-clinical posterior subcapsular lens changes (3.6%), greatest among males 12-17 years old at the time of examination, was noted in ~1,000 exposed children, compared to 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 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 posterior subcapsular 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.

(273) 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 to 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. The LOCS II lens opacification classification criteria was 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 to 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 at 1 Gy of 1.50 (95% CI, 1.15-1.95) for cortical opacities and 1.49 (95% CI, 1.07-2.08) for PSC. In contrast, no dose response was noted for nuclear lens changes. Overall uncorrected excess relative risk for cortical or posterior subcapsular 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.

(274) Another screening study of 20 persons 30-45 years after being treated for skin haemangioma in infancy noted pre-cataractous 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).

(275) A study of a paediatric population accidentally exposed while living in ^{60}Co-contaminated apartment indicated an odds ratio of 1.18 at 1 Gy for non-clinical lens changes (Chen et al., 2001). Mean exposure of 170 mGy was noted in this population although doses ranged from 1-1,200 mGy. Annual ^{60}Co exposures of >5 mGy/yr, in some cases for more than 10 years, were reported. A very recent follow-up of some of these children after a second ophthalmology examination, all still less than 23 years old, indicated that radiation induced lens changes, measured as sub-clinical focal lens defects (FLD), continued to increase in size and number 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 those of posterior FLD. The progressive nature of such changes five years later, in a paediatric population now removed from the contaminated environment, supports their 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 ~ 200 mSv and median value of ~ 54 mSv (personal communication from Dr. Muh-Shy Chen), for observing an increase in total FLD score five years later, were well within other reported threshold doses for radiation cataract.

Patients treated for Tinea Capitis

(276) In the first half of the twentieth century, before the development of modern of antifungal medications, ringworm of the scalp (tinea capitis) was often treated by epilation using X-ray doses ranging from 3.0-3.8 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 two hundred thousand 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 ~11,000 Israeli immigrants (e.g., Modan et al., 1977; Ron et al., 1988) and ~2,000 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 patient's eyes were often shielded with lead foil, recreation of the original treatment procedures indicated the lens received doses ranging from 0.2-0.8 Gy (Schulz and McCormick, 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.

(277) From 1964-1965, approximately15 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 to 1.0. Thirteen cases of "posterior subcortical opacities" were noted in exposed individuals compared to 2 cases in unirradiated controls. An estimated OR of 5.9 was calculated (Shore and Worgul, 1999). A second follow-up from 1968-1973, based on a mail survey roughly 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.

U.S. Radiation Workers

(278) Recently, Jacobson reported an increased incidence of posterior subcapsular opacities in retired nuclear plant uranium processing workers at three United States Department of Energy facilities (Jacobson, 2005). Cataract type was documented by telephone interview with each person's ophthalmologist while transuranic body burdens from 0-600 mSv were calculated from individual dosimetric records maintained by each installation. There were 97 subjects with a median age of 76 in the study and 20.6% of these were reported to have posterior subcapsular cataracts (most were bilateral). The median recorded dose for all cases was 168 mSv compared to 89 mSv for subjects without PSC. A significantly increased number of cases was noted for subjects exposed to >200 mSv (37.5%) compared with lower exposures (15.1%).

(279) In contrast to this study, a much earlier study by Voelz (1967) of ~850 nuclear reactor workers of relatively young ages (<40 yrs) 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 cataract was 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 mSv) with a mean of 4 rem across all age groups. Of note, minor lens changes (posterior subcapsular opacities, vacuoles and polychromatic plaques) which 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 aging and not radiation effects. The dosages to which these workers were exposed was considerably lower than that of the later Jacobson study and the average age at examination was some 20 years younger so comparisons between the two groups are difficult.

(280) 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" where he was potentially exposed to external beta, gamma and fast neutrons as well as inhalation hazards from plutonium, his recorded film badge total occupational whole body dose was 67 rem and eye lens dose 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 was 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 iris and ciliary body, in close contact to the lens, and that this exposure was the contributory factor in his cataract development.

Astronauts

(281) Data from the US astronaut corps (Cuccinotta 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 cataract, although the quality and energies of space radiation exposures are fundamentally different from those occurring on earth.

(282) Most recently, Chylack and coworkers (2009) reported preliminary results from the NASA Study of Cataract in Astronauts (NASCA) 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 U.S. astronauts that have flown in space to a well-matched control population of 247 astronauts and/or military aviators that have not flown such missions. Of concern, only roughly 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 least likely to receive significant cataractogenic doses or be exposed to potentially more damaging heavy ions.

(283) 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.

(284) The authors reported that variability and median of cortical cataracts were significantly higher for exposed astronauts than for non-exposed astronauts and comparison subjects with similar ages ($p = 0.015$). 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 relation between PSC size and exposure was noted in the astronaut core. Nuclear cataract was not associated with space radiation exposure. The authors concluded that cataract risk for cortical and posterior subcapsular opacities may be increased at small radiation doses.

Medical Workers and Interventional Radiologists

(285) UNSCEAR (2000) reported that exposure to X-rays in interventional medical workers and radiological technicians are 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 (Vano et al., 2008; Kim et al., 2008; Ubeda et al., 2010). With an exponential rise 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 (Vano et al., 1998). Several studies in these groups of occupationally exposed individuals offer support for this hypothesis.

(286) A pilot study of interventional radiologists 29-62 years old, reported that prevalence and severity of posterior subcapsular cataracts was associated with age and years of practice (Junk et al., 2004). Reconstructed yearly dose estimates of lens exposure ranged from 450-900 mSv. These exposures are consistent with reported exposures of similar medical workers (Vano 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 5/59 had clinically significant posterior subcapsular cataracts. However, there was no age-matchedcontrol group in this study, so the effects of aging versus radiation exposure are unclear.

Interventional Cardiologists

(287) X-ray exposure to the lens of the eye of interventional cardiologists and other paramedical personnel working in catheterisation laboratories are high and could result in radiation-induced lens changes. A recent pilot study to investigate this was organised by the International Atomic Energy Agency (IAEA) (Kleiman et al., 2009; Vano 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, posterior subcapsular opacities were found in 38% of cardiologists and 21% of paramedical personnel compared to 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 relative risk of posterior subcapsular opacities in interventional cardiologists, as compared to 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 relative risk is unlikely to be attributed to age, as only a very modestly increased age-related risk for PSC has been noted in the literature and PSC represent only a small fraction of lens opacities at any age.

(288) 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 prevalence of posterior lens opacities was noted for cardiologists 29/56 (52%) (P<0.001) and nurses 5/11 (45%) (P<0.05) compared to age and sex matched unexposed controls (2/22, 9%). Relative risks for lens opacification were 5.7 (95% CI 1.5-22) for cardiologists and 5.0 for nurses (95% CI 1.2-21). 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).

(289) The authors of both publications suggested that 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.

Radiologic Technologists

(290) A well designed, prospective analysis, with 20 year follow-up, of 35,700 radiological technicians, 22-44 years old at the onset 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 confounder variables, such as estimated sun exposure, obesity, diabetes, hypertension and arthritis were also analysed. The study results indicated that having ten or more diagnostic X-rays, particularly to the face or neck, was significantly associated with increased risk of cataract. 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 60 mGy) had an adjusted hazard ratio of 1.18 (95 % CI: 0.99, 1.40) compared with individuals in the lowest category of occupational lens exposure (mean 5 mGy), although the dose-response trend was not statistically significant. The median occupational radiation dose to the lens was estimated to be 28.1 mGy for the entire cohort. Significantly, the association between radiation exposure and self-reported cataract was strongest among technologists diagnosed before 50 years old. 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 development in these individuals. It is noted that no statistically significant associations were seen for cataract extraction incidence, however.

Conclusions

(291) 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 8 Gy for visual impairment (ICRP 1991, 2007) may underestimate risk. Some of the earlier epidemiological studies, on which the 2001 and 2007 guidelines are based, 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 better dosimetry,

may be factors which contributed to more recent findings of radiation cataract risk at low exposures. Continued follow-up of A-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 cataract

(292) Studies with animals offer the opportunity to examine the effects of precisely controlled radiation exposures on specific pathologies. One such model utilises 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).

(293) 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.

(294) Recent findings demonstrate dose-related significant lens opacification within a reasonable fraction of the lifespan of the mouse or rat after exposure to as little as 100 mGy X-rays or 32.5 cGy ^{56}Fe (Worgul et al., 2005 a,b). For example, 4 week old rats were irradiated with doses of either 100 or 500 mGy of 250 kVp X-rays and lens changes were followed by weekly slit lamp examination for 64 weeks (~35% of average lifespan) using a modified Merriam/Focht radiation cataract scoring method (Figure 2.9). At 64 weeks post-exposure, more advanced cataracts (grades 1.5 and 2.0) were only just beginning to appear in the 500 mGy whole lens irradiated group with a prevalence of 0.1 each.

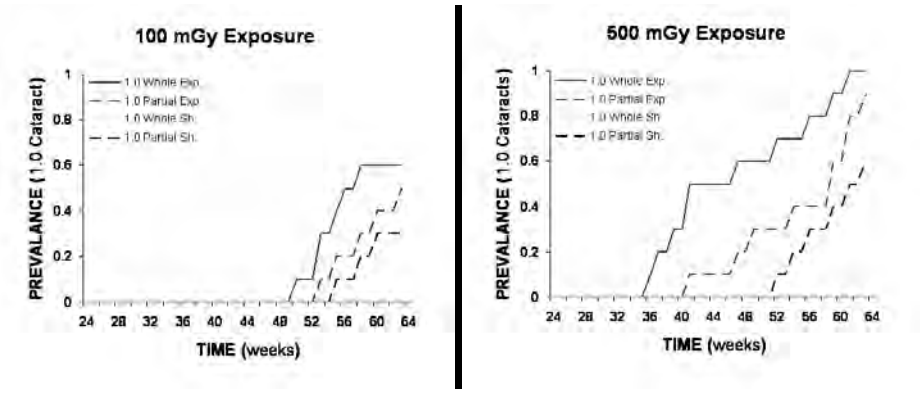

Fig. 2.9. Prevalence estimates as a function of time post-irradiation for radiation cataract grades 0.5 and 1.0 following 100 mGy or 500 mGy irradiation. The figures show early opacification in lenses totally exposed without any lead shielding (Whole Exp.), totally shielded lenses (Whole Sh.) and the shielded (Partial Sh.) and unshielded (Partial Exp.) portions in half-shielded lenses (Worgul et al., 2005a).

(295) This animal study used doses far lower than the presumptive threshold dose for cataracts. The fact that 100 mGy X-rays is cataractogenic within a third of the lifespan 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 100 mGy of X-rays produces measurable lens opacification within a third of the life span of the rat and suggests that lower doses may also be cataractogenic.

(296) Animal models are also important in helping determine the pathology, molecular mechanisms and biochemistry underlying radiation cataract (Blakely, 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).

(297) In a similar fashion, for more than 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).

(298) 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 estrogen in ^{60}Co 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 cataract is significantly greater for females than for males (EDPRG, 2004; Klein et al., 2008).

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

Mechanisms of damage

(300) 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 (Jose, 1978; Worgul and Rothstein, 1975; Worgul et al., 1989). Although the precise mechanisms of radiation cataract 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. 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

(301) 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 FGF and CDK (Chang, 2005; 2007), extracellular matrix protein production (McNamara et al., 2001; Chang, 1007) 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

(302) 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).

(303) 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 sub-populations. This includes the recently reported increase in cataract prevalence in mice haploinsufficient for both ATM and MRAD9 (Kleiman, 2007).

(304) Inclusion of such radiosensitive sub-populations 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 Cataract

(305) Oxidative stress is believed to be a major early or initiating event in the development of cataract 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 cataract (Giblin et al., 1995; Kleiman et al., 1990; Kleiman and Spector, 1993; Spector et al., 1995; 1998; Zigler, Jr. et al., 1989). 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; Giblin, 2000; Kleiman et al., 1990) (Spector et al., 1995).

DNA Damage and Cataract

(306) Because DNA is so easily damaged by oxidative stress or direct photochemical action of ultraviolet light, many investigators have suggested that unrepaired DNA damage to the lens epithelium ultimately results in cataract (Bellows and Bellows, 1975; Jose 1978; Bloemendal 1984; Courtois et al., 1981; 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; (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 posterior subcapsular opacification.

(307) 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 cataract (Worgul et al., 1991), (b) the increased frequency of DNA single strand breaks in the epithelium of some patients with cataract (Kleiman, 1993), (c) the relationship between low or high-LET irradiation and the development of posterior subcapsular cataracts (Worgul et al., 1976) and (d) the association between bilateral cataract and human genetic diseases involving defects in DNA repair mechanisms such as Cockayne syndrome (Nance and Berry, 1992), 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

(308) New data from animal models and from exposed human populations suggests that lens opacities occur at doses far lower than those generally assumed to be cataractogenic and these observations are consistent with the presence of only a small dose threshold, and even with its absence. Recent occupational findings in chronically exposed workers suggest long term risk for cataract and 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 reassessment. 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

(309) The respiratory system includes nasopharynx, pharynx, larynx, trachea, bronchi and lungs. Inspired and expired gases are transported from the nasopharymx 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 they are the functional sub-units of the respiratory system, being the sites of gaseous exchange between the atmosphere and the blood.

(310) 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.

(311) Gas exchange is between type-I pneumocytes, basal membrane and capillary endothelium. Type-II pneumocytes produce a surfactant, which 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 inter-alveolar walls, which are composed of loose connective tissue with capillaries, elastic, collagen and reticular fibres

(312) Proliferation rates in the normal adult lung are very low, with LI less than 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 >5-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

(313) Toxicity in the respiratory system is fairly common after thoracic irradiation for cancer of the lungs, breast, oesophagus and haematologic malignancies, where large volumes of lung are irradiated. Clinical symptoms of acute radiation injury, which develops during the first 1-3 months after radiotherapy, include dyspnoea, cough and fever, characterised as radiation pneumonitis. Symptomatic pneumonitis occurs in about 5-10% of patients irradiated for mediastinal lymphoma or breast cancer, with higher incidences in lung cancer patients (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.

(314) Chest radiographs and computerised tomography (CT) images are used to detect both radiation pneumonitis and fibrosis, with CT scans being most sensitive (Ikezoe et al., 1988; Mah et al., 1986; 1987). 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% breast cancer patients and >60% mediastinal lymphoma patients (McDonald et al., 1995). Scintigraphic techniques have also been extensively used to investigate functional changes (perfusion and ventilation) in irradiated lungs (Boersma et al., 1993; Marks et al., 1993; Prato et al., 1977). 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 about 10-40 weeks.

Dose response relationship

(315) The most important factors determining the development of radiation pneumonitis and fibrosis are total exposure 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 per day (Bentzen et al., 2000). Clinical data from total body irradiation with bone marrow replacement in leukaemia patients, or from half body irradiation for control of pulmonary metastases, show that the ED_1 for lethal pneumonitis is 7-8 Gy, with a ED_{50} 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).

(316) Fractionated exposure of whole lung also leads to considerable sparing. This is consistent with the relatively low α/β ratio of about 3-4 Gy determined from both clinical (Bentzen et al., 2000; Dubray et al., 1995; Van Dyk and Keane 1989) and animal studies (Herrmann et al., 1986; McChesney et al., 1989; Parkins and Fowler 1986; Van Rongen et al., 1993; Vegesna et al., 1989). Clinically significant (symptomatic) radiation pneumonitis is uncommon in adults after total doses of <20 Gy in 2 Gy fractions, with ED_5 and ED_{50} 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 and compliance may be seen in young children after lower doses to developing lung (Benoist et al., 1982; Wohl et al., 1975).

(317) For the complex 3-D treatment planning regimes used in modern curative radiotherapy of solid tumours, there is a 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 take into account the influence of fractionation schedule and to estimate the relationship between the 3-D 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 (NTD), which is the total dose in 2 Gy fractions that is biologically equivalent to the actual delivered dose, according to the LQ model (Newcomb et al., 1993; Van Dyk and Keane 1989). The complex 3-D treatment plan is then summarised using a dose volume histogram (DVH), which can be reduced to a single parameter and related to the normal tissue complication probability (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) or lung volume irradiated to >20 Gy (e.g. Graham et al., 1999; Marks et al., 1997; Kim et al; 2005). Such approaches have shown that mean lung doses >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 (Figure 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).

(318) A disadvantage of reducing 3-D 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 (Novakova-Jiresova et al., 2005; Travis et al., 1997; Van Luijk et al., 2005).

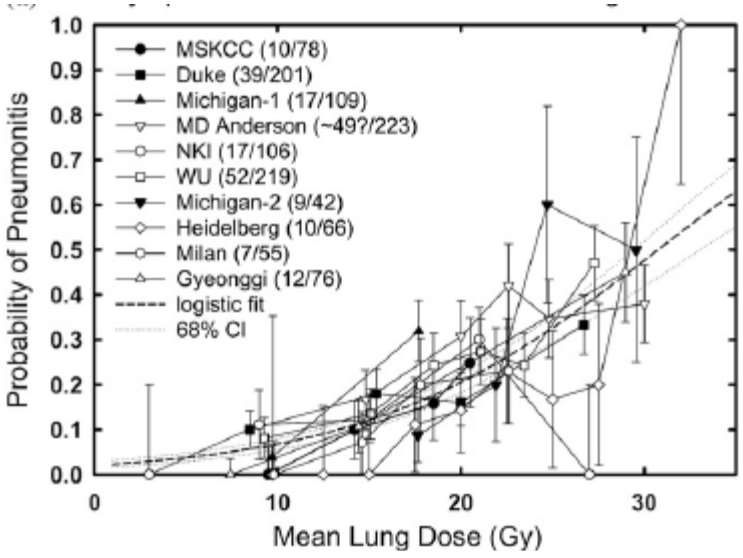

Fig. 2.10. Rate of symptomatic radiation pneumonitis after fractionated partial lung irradiation related to mean lung dose. For full references of data used, see original Figure 2 in Marks et al. (2010a).

(319) The relationship between radiation dose and structural lung damage was studied extensively by Mah and Van Dijk (Mah et al., 1987; Van Dyk 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 Gy, 34 Gy 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 FSU (functional sub-units), such as lung, is related to the number of FSU 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.

(320) 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 (Hrafnkelsson et al., 1987; Lagrange et al., 1988; Mehta, 2005; Seppenwoolde et al., 2003). Experimental studies in mice indicate a substantial modifying effect, with DMF 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 and co-morbidity, or biological parameters

e.g. levels of circulating cytokines, and the risk of damage, although results are not always consistent (Mehta, 2005).

(321) One particularly interesting debate surrounds the predictive value of plasma TGFβ levels in identifying patients most likely to develop lung damage after radiotherapy. TGFβ has been shown to play an important role in the development of radiation-induced pneumofibrosis in various animal models (see 2.7.3). Several clinical studies have also shown that persistently elevated plasma TGFβ, 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 TGFβ 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 showed that mean lung dose was significantly correlated with the plasma TGFβ levels 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 TGFβ 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

(322) 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 (Fleckenstein et al., 2007; Gross 1980; Phillips and Margolis 1972).

(323) Damaged EC and type II pneumocytes, as well as activated macrophages, also produce increased levels of various inflammatory mediators, which 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, which 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 increasing number of macrophages and other inflammatory cells (Lehnert et al., 1991; Travis, 1980). 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. A 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 EC), increased microvascular permeability and increased production of inflammatory cytokines. The functional consequences of this are a dose dependent increased breathing rate (Travis et al., 1979) and lethality after single doses in excess of 11 Gy (Travis and Tucker, 1986).

(324) 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 multi-cellular interactions between the pneumocytes, EC, fibroblasts and macrophages are involved in both initiation and maintenance of the fibrotic response (McDonald et al., 1995; Morgan and Breit 1995; Rubin et al., 1992; Wall and Schnapp, 2006).

(325) TGFβ in particular, plays a key role in the development of pneumofibrosis, via accelerated terminal differentiation of progenitor fibroblasts to fibrocytes (Burger et al., 1998; Finkelstein et al., 1994; Hill, 2005). Experimental models of thoracic irradiation have demonstrated dose-related increased expression of TGFβ preceding lung fibrosis (Finkelstein et al., 1994; Rube et al., 2000). Radiation-induced increases in TGFβ 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 TGFβ comes from studies showing that inhibition of TGFβ signaling inhibited radiation-induced activation of TGFβ in irradiated lungs and decreased both the inflammatory and fibrotic response to radiation (Anscher et al., 2006; 2008; Rabbani et al., 2003). 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.

(326) 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 sub-tolerance initial irradiation (Terry et al., 1988), although many of the animals subsequently succumbed 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 about 0.5 Gy per day, for acute pneumonitis, whereas no time factor has been demonstrated for late fibrosis (Bentzen et al., 2000).

(327) 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; McChesney et al., 1989; Parkins and Fowler 1986; 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 0.7-1.2 hours (Parkins et al., 1988; Travis et al., 1987; Van Rongen et al., 1990 a, 1990b; Vegesna et al., 1989). Some studies have identified two components of repair, with a fast time $T_{1/2}$ of 0.4 hours dominating the effect and a slow component with $T_{1/2}$ of 4 h (Van Rongen et al., 1993).

2.7.4. Non-therapeutic exposures

(328) Analysis of data from the Japanese A-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 were given bone marrow transplants after exposure to doses of 5.6 to 13.4 Gy (Baranov et al., 1989). Additional reports indicate a high incidence of pulmonary infectious complications in post-mortem lung specimens of Chernobyl accident victims (Vlasov et al., 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

(329) 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; Newman et al., 2005; Okladnikova et al., 2002) and in experiments on animals (Brooks et al., 1992; Koshurnikova et al., 1972; Muggenburg et al., 1988). Studies conducted in Rocky Flats have shown an increased risk of pneumofibrosis at lung doses in excess 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 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.

(330) A typical feature of PP is the occurrence of fibrosis predominantly in the upper parts of the lungs (Okladnikova and Guskova 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 in 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).

(331) Macrophages that have absorbed radionuclides like ^{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, 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 (Guskovava 2004; Wall and Schnapp 2006).

2.7.5. Summary

(332) Symptomatic lung toxicity is common in patients irradiated for cancer of the lung, breast, oespohagus 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 TGFβ, 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, like genetic pre-disposition, co-morbidity and additional chemotherapy, may modify these risks.

2.8. Urinary Tract

2.8.1. Anatomical features and proliferative organisation

(333) 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

(334) The kidneys are paired organs, with their basic functional subunits, 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), 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 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 resporption is maintained via the juxta-glomerular 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.

(335) The adult kidney is a slow-turnover tissue, with low levels of proliferation in both tubular cells and glomeruli (LI <0.5%). However, the kidney is capable of responding to surgical or chemical injury by transient increased proliferation, lasting less than 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 to 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

(336) 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 3 to 5 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.

(337) 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).

(338) 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. By contrast, stimulated proliferation of irradiated rodent bladders does not begin until about 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 to 9 months (Stewart, 1986; Stewart and Williams 1991). Studies of Stewart and coworkers showed that the 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 exposure doses

Kidney

(339) 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 1950's (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, gave 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 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 greater than 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) (Figure 2.11).

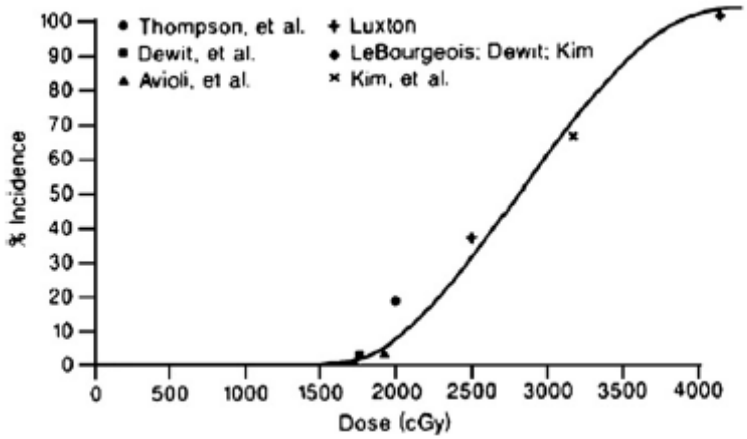

Fig. 2.11. Dose response for symptomatic kidney injury after bilateral kidney irradiation. (Reproduced from Dawson et al., 2010).

(340) 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 (Cassady, 1995; Stewart and Williams 1991). 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 ischemia, or whether this occurs independent of circulating renin levels.

(341) 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 ED_{50} 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, fractionated) progressed at a rate of about 1-2% per month relative to the contralateral kidney (12-13 Gy), decreasing to 60% of pre-treatment 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 about 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.

(342) Total body irradiation (TBI) combined with bone marrow transplantation (BMT) was commonly used in the 1980s and 1990s for treatment of various haematopoietic cancers, although it 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 (Lawton et al., 1991; 992; Lonnerholm et al., 1991; Rabinowe et al., 1991; Tarbell et al., 1988). The onset of nephropathy after TBI is generally shorter (<1 year) than after abdominal irradiation. In addition to typical symptoms of radiation nephropathy, haemolytic uremic syndrome is often seen, implicating the glomeruli as the principal site of damage. These patients usually receive pre-transplant conditioning with chemotherapy and immunosuppressive drugs, which significantly increase the risk of renal injury (Cheng et al., 2008). However, the damage is clearly related to radiation dose and the actuarial 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 7 fractions (Lawton et al., 1991; 1992).

Bladder and ureters

(343) 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 to 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 (Marks et al., 1995; Rubin and Casarett, 1972; UNSCEAR, 1982; 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).

(344) 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 about 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).

(345) 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 ischemia. The formation of calcareous deposits may also occur. These changes are normally seen within 2 to 3 years of irradiation and can result in permanent reduction of the bladder capacity, in some cases requiring total cystectomy.

(346) The ureters are more resistant than the bladder, and considerably more resistant than the small bowel, which is in close proximity. The incidence of uteric obstruction after doses of 60-70 Gy (in 2 Gy fractions, without

previous trans-urethral resection) is <5 % (Marks et al., 1995). The relative resistence of the ureters to development of stenosis was also confirmed in experimental studies in dogs and rats (Gillette et al., 1989; Kinsella et al., 1988; Knowles and Trott 1987). However, urothelial biopsies taken from Ukranians 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 area 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

Kidney

(347) Experimental studies demonstrate progressive, dose-dependent decreases in renal function after local irradiation or 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 in excess 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 (GFR) and renal plasma flow (ERPF) (Robbins and Bonsib 1995), and increased production of low osmolality urine (Stevens et al., 1991; Williams and Denekamp 1983) 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).

(348) Doses associated with severe functional impairment at >9 months after irradiation are in the range of 7-9 Gy, single dose. 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 was 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 new born beagle pups to TBI doses of only 2.2-3.6 Gy (Jaenke and Angleton 1990).

(349) 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 (Otsuka and Meistrich 1990; Robbins et al., 1994; Withers et al., 1986). The lack of functional recovery in the kidney is especially apparent in experimental systems where kidneys were re-irradiated after low initial doses, insufficient to produce renal impairment in < 1 year (Robbins et al., 1991; Stewart et al., 1988; 1989; 1994; Stewart and Oussoren 1990). 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.

(350) 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 <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, with leucocyte 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 (Robbins and Bonsib 1995; Stewart et al., 2001; Weshler et al., 1988). 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 (Robbins and Bonsib 1995; Stewart and Williams 1991).

(351) 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 (Joiner et al., 1992; Stewart and Williams 1991). Estimates of repair half times are in the order of 1.3-2 hours (Joiner et al., 1993; Van Rongen et al., 1990a). For doses per fraction <1-2 Gy, using more than one fraction per day, deviations from the LQ model have been shown (Stewart et al., 1987b). This deviation can partly be explained by incomplete repair during short inter-fraction intervals of <6 hours, although reduced induction of molecular repair mechanisms at low doses per fraction may also contribute (Joiner and Johns, 1988).

(352) Cisplatinum is sometimes given in combination with abdominal irradiation, e.g. for cervical and testicular cancers. Increased renal toxicity is a concern here, since cisplatinum is known to cause degeneration and necrosis of proximal convoluted tubules. Renal toxicity occurs within one week of ciplatinum administration but usually resolves within 1 to 3 months, unless very high doses have been given. Cisplatinum, given before or after irradiation, also significantly increases the late renal toxicity, particularly when the drug is given after irradiation (Moulder and Fish, 1991; Stewart et al., 1987a; 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 low to moderate dose renal irradiation was found to be much more toxic than the reverse sequence.

Bladder

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

(354) During the acute phase, reduced bladder capacity and increased urination frequency are seen, with a threshold single dose (ED_1) of >10 Gy and ED_{50} (dose to give a specific response in 50% of animals) of about 20 Gy (Dorr and Beck-Bornholdt 1999; Dorr and Schultz-Hector 1992; Stewart et al., 1991). This early damage is not associated with marked necrosis or loss of urothelium (Dorr et al., 1998; Stewart 1986), 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).

(355) The highly specialised, polyploidy 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 COX2 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 ICAM-1 expression in the microvascular endothelial cells is involved in triggering the early, inflammatory response (Jaal and Dorr, 2005).

(356) From 3-6 months after irradiation of mouse bladders, urothelial cell denudation is seen, with increased proliferative activity in remaining epithelial and endothelial cells, leading to multifocal atypical hyperplasia. The superficial cells loose 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 TGFβ immuno-reactivity and collagen deposition (Jaal and Dorr 2006c; Kraft et al., 1996; Stewart, 1986). Bladder calculi develop in mouse bladders 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 (Lundbeck et al., 1993; Stewart et al., 1978; 1991).

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

(358) Pelvic irradiation is sometimes given in combination with drugs like 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 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 cycophosphamide 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). Cisplatinum is not specifically toxic to the bladder when used alone, but does significantly increase both the early and late radiation damage (Lundbeck et al., 1993; Lundbeck and Overgaard 1992).

(359) 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 that this did not increase the sensitivity to subsequent irradiation (Post et al., 1995).

2.8.4. Summary

(360) 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 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.

(361) Radiation tolerance of the bladder is considerably higher than for 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 about 6 to 12 months, resulting in permanent reduction in bladder capacity.

2.9. Musculoskeletal system

2.9.1. Anatomical features

(362) 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%.

(363) 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.

(364) 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 that are then invaded by osteoblasts that deposit collagen and hydroxyapatite along the cartilage matrix.

(365) 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.

(366) 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 exposure doses

(367) 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 on the presence of other tissue pathology, such as, decaying teeth, infection, or tumours.

(368) 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 to > 55 Gy (Karasek et al., 1992).

(369) 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 in excess of 60-65 Gy are used (Cooper et al., 1995; Fajardo et al. 2001). Emami 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) (Emami et al., 1991). For impaired function of the temporo-mandibular joint, the equivalent estimated doses are 60 Gy (ED 5/5) and 72 Gy (ED 50/5).

(370) 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 1.8-2.8 (Hopewell, 2003; Overgaard, 1988).

(371) In contrast to mature bone, growing bone is among the most radiosensitive of all tissues (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 $ED_{5/5}$ doses 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 A-bomb survivors from Hiroshima and Nagasaki also show significant age-dependent growth retardation in individuals of both sexes who were below 19 years of age at the time of bombing (Nakashima et al., 2002).

(372) 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 in that 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 about 55 Gy (2 Gy fractions) has been estimated (Karasek et al., 1992).

2.9.3. Experimental data and mechanisms of damage

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

(374) 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 post-irradiation growth delay may be related to decreased local expression of parathyroid hormone-related peptide (PTHrP) and/or Indian hedgehog (IHh), key regulators of growth plate chondrocytes (Bakker et al., 2003; Damron et al., 2004; Pateder et al., 2001).

(375) 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 preoperative 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 total body irradiation, with or without bone marrow transplantation, suggests that postmitotic osteoclast precursor cells are of haematopoietic origin (Hosokawa et al., 2007). Because irradiation affects bone viability, the stability of surgical implants is also significantly reduced in irradiated compared to un-irradiated minipig bone (Verdonck et al., 2008), although the literature differs on whether the impairment is clinically significant or not (Colella et al., 2007; Nishimura et al., 1998).

(376) 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 is estimated to be about 4 Gy (Gillette et al., 1995). Whereas the multinucleated myofibers 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 myofibers or with each other to form new myofibers (Sabourin and Rudnicki 2000; Schultz and McCormick 1994). 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 post-irradiation hematopoietic reconstitution (Pang, 2000).

2.9.4. Internal exposure

(377) 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.

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

(379) The long term effects of various Ra (radium) isotopes have been extensively studied (Schmitt and Zamboglou, 1990). For example, late radiological lesions, including bone infarction, aseptic necrosis and patchy sclerosis, are seen with a total body ^{226}Ra burden in excess 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 relationship 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 in excess of 20 Gy or after ^{239}Pu doses greater than 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

(380) 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 low doses of radiation. Hence, while musculoskeletal radiation effects are a minor issue in most adult cancer patients, they remain a major problem in childhood cancer survivors.

2.10. Endocrine system

2.10.1. Anatomical features and functional organisation

(381) The endocrine system is an integrated system of small organs that involve the release of extracellular signaling 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 like water-salt metabolism, inflammatory and immune reactions and reproductive function, via secretion of hormones (e.g. growth hormone (GH), prolactin (LTH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle stimulating hormone (FSH). The cells of the APUD-system (Amine Precursor Uptake and Decarboxilation) 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 islets of Langerhans of 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.

(382) 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

(383) Cranial irradiation for brain tumours, nasopharyngeal carcinoma, ALL (acute lymphocytic leukaemia) or total body irradiation in preparation for bone marrow transplant, may lead to hypothalamic-pituitary dysfunction (hypopituitarism) and multiple pituitary hormone deficiencies (Agha et al., 2005; Schneider et al., 2006; Toogood 2004). 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. Growth hormone is the most vulnerable anterior pituitary hormone to irradiation, followed by gonadotrophin, corticotrophins and thyrotophin (Gleeson and Shalet, 2004; Littley et al., 1989). Isolated GH deficiency may develop 10 or more years after fractionated doses of 10-12 Gy (Brennan and Shalet, 2002; Holm et al., 1996), while higher doses (over 60 Gy in 2 Gy fractions) may produce hypopituitarism (Darzy and Shalet, 2003). 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 (Agha et al., 2005; Heikens et al., 1998).

(384) Cranial irradiation of childhood brain tumours, with fractionated doses in excess of 30 Gy in 2 Gy fractions, results in growth hormone deficiency and impaired growth in most patients manifesting within two 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, for the treatment of ALL between 1971 and 1990 in the UK, was associated with GH deficiency in up to 50% of cases. Total body irradiation, with lower doses of radiotherapy (7.5-15.75 Gy fractionated) may also be associated with pubertal GH insufficiency, thyroid dysfunction and radiation-induced skeletal dysplasia.

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

(386) Hyperprolactinemia can result from irradiation of the hypothalamus at fractionated doses > 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 fractionated doses), due to damage to the ventromedial hypothalamus and GH deficiency (Cohen 2003). No relationship between deficiency of anti-diuretic hormone (ADH) and irradiation of the cranium has been reported. Radiation-induced central diabetes insipidus is very uncommon.

(387) 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 ovogenesis and spermatogenesis) and hypothyroidism were only seen at doses of over 150 Gy accumulated dose. Hyperplastic and dystrophic changes (nuclear pyknosis and lysis, disorientation of the layers of the glomerular and fascicular zones and presence of bi-nuclear and giant cells) were also seen in the adrenal glands of these animals (Shvedov and Akleyev, 2001).

2.10.3. Thyroid and parathyroid disorders

(388) 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 below 40 Gy. However, there is some evidence to suggest that lower doses may be associated with clinically significant but subtle damage to thyrotophin 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 >18 Gy (Cohen, 2005), most commonly presents as hypothyroidism, with low T_4 and elevated TSH. Risk factors are radiation dose, female sex, and older age at diagnosis, with the highest risk occurring at 5 years after irradiation (Sklar et al., 2000). Hyperthyroidism may also develop from about 8 years after fractionated irradiation at doses >35 Gy, but this is less common (Sklar et al., 2000) (Hancock et al., 1991). Chemotherapy is an independent risk factor for thyroid dysfunction and may potentiate radiation-induced damage.

(389) Autoimmune thyroiditis has been studied among persons exposed to low to moderate doses of external radiation or radioactive iodines, but the results have been inconsistent (Nagataki et al., 1994; Imaizumi et al., 2006; Davis et al., 2004; Volzke et al., 2005; Tronko et al., 2006; Agate et al., 2008). Recent studies of populations exposed to ^{131}I 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).

(390) Both external radiation involving the neck and radioactive iodines confer an increased risk of developing benign thyroid nodules including adenomas, focal hyperplasia and colloid nodules. A dose-response relation 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), from the Chernobyl accident in Ukraine (Zablotska et al., 2008) and from fallout from nuclear weapons testing in Kazakhstan (Land et al., 2008).

(391) 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 γ-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).

(392) 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 relation was observed in following childhood radiation treatment for benign diseases of the head and neck (Schneider et al., 1995).

2.10.4. Hypothalamic-pituitary-adrenal axis

(393) 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 adrenal gland weight 5 years after whole body irradiation with doses of 21-125 cGy/yr) (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 was seen in the glomerular zone at total doses >375 cGy, which may be compensatory in nature and be responsible for the development of primary aldosteronism 3-5 years after irradiation.

(394) 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 in excess of 50 Gy (Littley et al., 1989). The insulin tolerance test is regarded as the gold standard for assessing the integrity of the hypothalamo-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

(395) Survivors of childhood malignancies, particularly leukaemia and brain tumours are at risk obesity in adulthood. Children who received cranial irradiation (18-24 Gy fractionated doses) as part of their treatment for ALL have an increased body mass index (BMI) 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, life-style including lack of exercise, endocrine and neuro-endocrine) but hypothalamic damage resulting involving hyperinsulinism and altered leptin sensitivity may contribute. Obesity may also result from cranial irradiation (>51 Gy fractionated doses), due to damage to the ventromedial hypothalamus and GH deficiency (Cohen, 2003). Childhood cancer survivors treated with brain, total body or abdominal irradiation have an increased risk of diabetes that appears unrelated to body mass index or physical inactivity (Meacham et al., 2009). No relationship between deficiency of anti-diuretic hormone (ADH) and irradiation of the cranium has been reported.

(396) 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 BMI should be carried out routinely. Advice on healthy eating and exercise should be given early and reinforced regularly.

2.10.6. Hypothalamic-pitutary-gonadal axis

(397) 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 frequent aetiology. Fractionated radiation doses of 35-45 Gy are associated with increasinly impaired gonadotrophin after irradiation (Constine et al., 1993; Littley et al., 1989). 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 or cranial irradiation for brain tumours, and this is more profound in younger patients (Ogilvy-Stuart et al., 1994). To further complicate matters this early onset of puberty may be followed by the evolution of gonadotrophin deficiency, necessitating the judicious use of gonadotrophin analogues to suppress pubertal development. Early pubertal development is also associated with a premature growth spurt, early epiphyseal fusion and reduced final adult height.

(398) In contrast, low dose cranial irradiation (18-24 Gy; 2 Gy fractions) in 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).

(399) High-dose radiotherapy (fractionated doses >24 Gy) 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

(400) 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 –adrenal axes. The mechanisms of these types of are being increasingly understood, and they require replacement hormone therapies (see Chapter 3.3).

2.11. Nervous system

2.11.1. Anatomical features and proliferative organisation

(401) The nervous system is divided into a central part (CNS), comprising the brain and spinal cord, and 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.

(402) There are two major parenchymal cell types in the CNS, both of neuroectodermal origin: the neurons (structural and functional subunits 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 loose 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 PNC, Schwann cells are involved in myelination and regeneration of peripheral nerves and, in contrast to oligodendrocytes, each Schwann cell is connected to only a single myelin segment.

(403) 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 date on therapeutic exposure doses

Clinical syndromes

(404) Radiation injury to the CNS can have devastating consequences and hence conservative dose limits are 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 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.

(405) 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 (Nieder et al., 2007b; Schultheiss et al., 1995; Tofilon and Fike, 2000; Wong and Van der Kogel, 2004). 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 with the severity of white matter changes (Constine et al., 1988) but can also occur in the absence of apparent structural lesions.

Tolerance doses

(406) 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 <50 Gy (2 Gy per fraction) are associated with a very small risk of radiation myelopathy (<0.5%) in the absence of chemotherapy or other predisposing factors (Marcus, Jr. and Million, 1990; Schultheiss, 2008; Schultheiss et al., 1995; Wong et al., 1994).

(407) Estimated doses for a 5% incidence of myelopathy are 57-61 Gy to the cervical cord (2 Gy per fraction) with a steep rise in the probability of damage above these doses (Figure 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).

(408) 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. (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 ED_5 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).

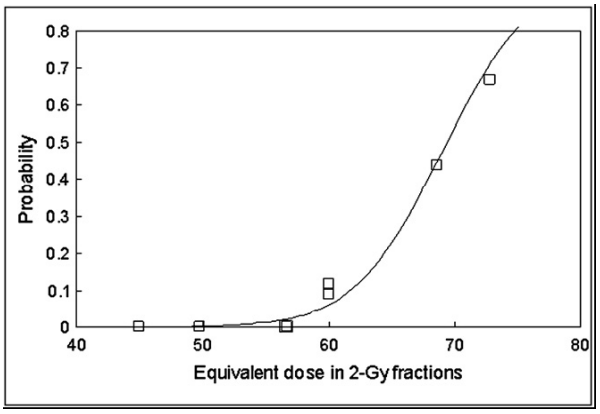

Fig. 2.12. Estimated probablility of exceeding cervical cord tolerance (myelopathy) as a function of total total iso-effective (equivalent) equivalent dose in 2-Gy fractions (Schultheiss, 2008).

(409) Brain necrosis in adults is rare for conventionally fractionated total doses of <60 Gy, although neurocognitive defects are seen at considerably lower doses. Cognitive impairment, including dementia, occurs in 20->50% of adult brain tumour patients who survive >1year after treatment with large field irradiation to total doses of 40-60 Gy (Crossen et al., 1994). Declines in IQ scores with time from treatment have been reported in children treated with ALL given low dose prophalactic whole brain irradiation (24 Gy in 2 Gy per fraction) and in children with brain tumours treated with cranial doses of 23-36 Gy, excluding tumour boost, (Langer et al., 2002; Mulhern et al., 1992; 2004). 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). Concommitant 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 socioeconomic 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 the cranial radiation doses (when comparing those with no cranial radiation, <50 Gy, >50 Gy total fractionated dose) for treatment of astrocytoma, glial tumours or ependymoma, but there was no clear dose response relationship for medulloblastoma.

(410) 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, Jr. et al., 1982). This is consistent with experimental studies showing that the spinal cord has a low α/β ratio of 2 Gy (see below). A recent analysis of radiation myelopathies estimated α/β ratios of <1 Gy for human cervical cord (Schultheiss, 2008).

(411) 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 about 15% when the interval between fractions is reduced from 24 to 6 hours (Schultheiss et al., 1995).

(412) Although it has been 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 like 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.

(413) By contrast, clear volume effects are discernable in irradiated brain, both for clinical side effects and changes in structure detected using neuroimaging (Levegrun et al., 2001). For example, after stereotactic radiosurgery for arteriovenous malformations (AVM) 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 radiosurgry (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 volume treated to >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 >70 cm^3 versus < 70 cm^3 (31% and 7%, respectively) (Santoni et al., 1998).

2.11.3. Experimental data and mechanisms of damage

Acute damage

(414) 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 in excess of 5 Gy (Mastaglia et al., 1976; Van der Kogel, 1986). This acute injury is preceded by increased inflammatory gene expression, e.g. NFκB, TNFα and IL-1β, which has been demonstrated within hours of irradiation of rodent CNS (Gaber et al., 2003; Hong et al., 1995; Raju et al., 2000; Tofilon and Fike, 2000; Wong and Van der Kogel, 2004). TNFα 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

(415) From about 4-6 months after high radiation doses (>20 Gy single dose) focal demyelination of the spinal cord develops (latency is inversely related to dose). This rapidly progresses to tissue necrosis and the onset of paralysis. Vascular lesions (oedema, thrombosis, 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

(416) Irradiation of whole brain with single doses as low as 4.5 Gy has been shown to significantly impair memory and motor functions in mice, whereas a dose of only 1.5 Gy caused 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 versus parenchymal targets for radiation injury

(417) The documented association between disruption of the BBB (or BSCB) and both acute and late radiation toxicity implicates endothelial cells

(EC) as important targets (Nordal and Wong, 2005; Rubin et al., 1994). Indeed, dose-dependent loss of EC has been demonstrated in irradiated brain and spinal cord within 24 hours of exposure (Li et al., 2004; Ljubimova et al., 1991). 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 EC apoptosis or disruption of the BSCB, whereas p53 knock out mice responded similarly to wild type mice. In contrast, the apoptotic response of oligodendrocytes (also seen within 24 hours of irradiation) was dependent on p53 and not ASMase (Chow et al., 2000; Li et al., 1996). Taken together, these results suggest that EC 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).

(418) The apoptotic response of oligodendrocytes, initiated within 24 hours of spinal cord irradiation, results in a dramatic loss of oligodendrocyte progenitors (O2A cells) at 2 to 4 weeks after single doses > 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 in humans is associated with Lhermitte's syndrome. 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 that delivered to the parenchyma or to O2A progenitor survival.

(419) 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 (EC, 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 EC leads to breakdown of the BBB and transient, acute CNS injury, whereas delayed mitotic EC death results in late onset breakdown of the BBB, white matter necrosis and permanent late CNS injury (Nordal and Wong, 2005; Wong and Van der Kogel, 2004).

Fractionation effects

(420) Extensive experimental data on the influence of fractionation schedules on radiation tolerance show that the spinal cord has a high capacity for repair of sublethal damage, with α/β ratios of about 2 Gy for cervical cord and 3-5 Gy for lumbar cord (Ang et al., 1983; Thames et al., 1988; Van der Kogel, 1986; White and Hornsey, 1978; 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. By contrast, the overall treatment time has little influence on tolerance dose in this slow turnover tissue, for single fractions per day, given in total times up to 8 weeks (Van der Kogel et al., 1982; White and Hornsey 1980). For multiple fractions per day, incomplete repair between fractions may lead to increased damage compared to single fractions per day. Analysis of repair half-times from experimental studies in rodents indicates bi-exponential repair kinetics, with fast and slow component $T_{1/2}$ values of 0.2-0.7 hours and 2.2-6.4 hours, 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 hours compared with 24 hours.

(421) 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) after partial tolerance initial doses increased to ≥ 140% of biologically equivalent tolerance doses in single course schedules (Ang et al., 1993; Wong and Hao, 1997). Additional monkey studies 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

(422) 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). The ED_{50} for myelopathy with 2 x 4 mm fields was the same as for a single 4 mm field, and considerably greater than for the 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.

(423) Studies in pigs and monkeys demonstrate a much smaller volume effects for field sizes of 1-10 cm, or 4-16 cm (Schultheiss et al., 1994; Van den Aardweg et al., 1995). In the monkey studies (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.

(424) Significant volume effects were seen in dogs for functional, neurological symptoms (pain, paresis) after irradiation of 4 cm or 20 cm lengths of spinal cord (ED_{50} 78 Gy 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 <5 Gy

(425) Between the years 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 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 2,215 irradiated subjects and 1,395 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 among 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 showed only borderline differences (Omran et al., 1978).

(426) 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).

(427) A population based cohort study of 3,094 men who were irradiated for cutaneous haemangioma before age 18 months reported that intellectual development was adversely affected by radiation doses >100 mGy (Hall et al., 2004). The proportion of boys attending high school decreased with increasing sose of radiation, from 32% among those not irradiated to 17% in those who received >250 mGy. Comparing these two groups, the multivariate odds ratio for high school attendance was 0.47 (95% CI 0.26-0.85) for irradiation to the frontal part of the brain, whilst for irradiation of the posterior brain it was 0.59 (0.23-1.46).

(428) 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.

(429) 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 up to 4 Gy at age 13 years or older (Yamada et al., 2009). The incidence of dementia was between 15 and 17 per 10000 person-years for exposure doses of 5 mGy, 5-500 mGy and >500 mGy.

2.11.5. Summary

(430) Spinal cord is relatively radioresistant, but the consequences of exceeding tolerance are so severe (paralysis) that conservative dose restraints 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 EC damage rather than dose delivered to the parenchyma and glial damage.

(431) Brain necrosis is rare after total fractionated doses <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 and late, progressive tissue damage.

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3. MODIFIERS OF NORMAL TISSUE RESPONSE

3.1. Terminology

(432) 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 most frequently 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 pre-clinical 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 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, for example, the heart.

(433) While the terminology is useful, it is important to keep a few details in mind. 1) 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. 2) The distinction among 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 post-radiation 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. 3) On the other hand, certain agents, for example, some immune-modulators and agents that exert a trophic effect on normal tissues, may actually have opposite effects when given before radiation exposure compared to 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

(434) Reactive oxygen species (ROS) are normally controlled by the antioxidant defense 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 (Gauter-Fleckenstein et al., 2008; Muscoli et al., 2003; Rabbani et al., 2007; Rong et al., 1999; Salvemini et al., 1999; Vujaskovic et al., 2002a), 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).

(435) 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 nuclear transcription factor κB (NFκB) 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).

(436) The high intrinsic radiosensitivity shown by some cell lines is associated with disturbed antioxidant activity (Tulard et al., 2003). Down-regulation of antioxidant enzymes is also a determinant in the process of neoplastic transformation. Both effects are related to decreased contents of 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 tissue against radiation damage (Prasad, 2005).

(437) An antioxidant can exert its action directly or indirectly. Antioxidants can directly scavenge hydroxyl radical, peroxyl radical, peroxynitrite 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, confering catalase-like behaviour to haeme 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).

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

(439) Induction of free radicals is one of the earliest cellular events that occur after ionising radiation and radical scavengers, like cysteine, have been recognised as potent radiation protectors for more than 50 years. These compounds are effective when given before irradiation and, since 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 more than 4,000 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 dephosphorylised 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 blood brain barrier, 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 is the maximum degree of radioprotection seen among normal tissues, ranging from protection factors of up to 3.0 in salivary gland to <1.5 in bladder and kidney. In addition to drug uptake and clearance rates and differential dephosphorylation activity among 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 preclinical data in rodent models and canine tumours have demonstrated significant levels of radioprotection, especially in smaller, non-hypoxic tumours and after fractionated irradiation (Andreassen et al., 2003; Denekamp et al., 1983; McChesney et al., 1988).

(440) 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 accessibility of ionisation sites by inducing DNA packaging. Side effects of amifostine include hypotension, vomiting and allergic reactions (Andreassen et al., 2003; Lindegaard and Grau, 2000).

(441) 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 minutes prior to each radiation exposure, high cost, side effects and lingering doubt as to the absence of tumor protection have hampered its widespread clinical use.

3.2.3. Inhibitors of apoptosis

(442) 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 it 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

(443) Irradiation causes excessive production of eicosanoids (prostaglandins, prostacyclin, thromboxane and leukotrienes), which are endogenous mediators of inflammatory reactions like vasodilation, vasoconstriction, vascular permeability, microthrombus formation and extravasation of leucocytes. 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 (GS) inhibit excess eicosanoid synthesis mainly by inhibition of phospholipase A_2 activity and synthesis, thereby inhibiting release of arachidonic acid (the precursor of prostanoids and leukotrienes) from cell membranes. Non-steroidal anti-inflammatory drugs (NSAID) work via inhibition of cyclooxygenase, which specifically catalyses prostanoid synthesis, without affecting leukotriene synthesis. Most NSAID are reversible competitive inhibitors of arachidonic acid binding to cyclooxygenase 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.

(444) 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.

(445) Eicosanoids are formed from polyunsaturated fatty acids (PUFA), which cannot be synthesised but are derived from the diet. There is some evidence that modifications in dietary PUFA can have a beneficial effect in irradiated tissues, by shifting the balance of eicosanoid synthesis in the anti-inflammatory direction (Hopewell et al., 1994 a, b; Moulder et al., 1998). In particular, gamma-linolenic acid inhibits the production of inflammatory leukotrienes and increases the production of prostaglandin E_1 and thromboxane A_1. Prostaglandin E_1 has anti-inflammatory, anti-thrombotic and vasodilatory properties and thromboxane A_1 does not have the pro-thrombotic properties of thromboxane A_2. Eicosapentaenoic acid also selectively increases prostaglandins at the expense of thromboxanes.

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

(446) The renin angiotensin system (RAS) plays a key role in regulation of haemodynamics in the kidney, lung and circulatory system. In this negative

feed-back loop, decreases in arterial blood pressure stimulate renin release by the kidney and this cleaves angiotensin to angiotensin1 (Ang I), which is converted by angiotensin converting enzyme (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 RAS, 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). Anti-hypertensive mechanisms may be involved in reducing established nephropathy but this can not 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.

(447) 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 NO (nitric oxide) activity in irradiated kidneys, and AII receptor antagonists prevent radiation-induced increases in TGFβ, 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 (AP1) and NF κB. 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 RAS inhibition in irradiated tissue include suppression of oxidative stress and suppression of aldosterone, which promotes fibrosis in non-irradiation models, or a direct inhibition of fibroblast proliferation (discussed in Moulder et al., 2007).

3.2.6. Growth factors and cytokines

(448) Haematopoietic and nonhaematopoietic growth factors (HGF, GF) 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 the anti-apoptosis protein BCLXl. 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 (Rieger et al. 2009) demonstrates that G-CSF and 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.

(449) 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, physiologic half-life and interaction with other stromal cells within the lineage or stem-cell-selective microenvironmental niche.

3.2.7. Modifiers of endothelial cell response

(450) 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 (Hauer-Jensen et al., 2004; Wang et al., 2002).

(451) 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.

(452) After lower, more clinically relevant radiation doses the predominant effects of radiation involves a shift in the thrombo-haemorrhagic balance toward the pro-coagulant state (it is slightly anticoagulant under normal circumstances), increased fibro-proliferative properties, and increased chemotactic and immune cell activating properties (Hauer-Jensen et al., 2004).

(453) Many “endothelial-directed” approaches have been investigated in the attempt to ameliorate toxicity in normal tissues (Wang et al., 2007; Ward et al., 1998). 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.

(454) One of the more promising endothelial-oriented protection strategies involves inhibition of the enzyme hydroxymethyl-glutaryl coenzyme A (HMG-CoA) reductase by drugs that belong to the class of 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

(455) Normal tissues generally are 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 to 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 dependence 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 chemo-radiosensitisation requiring between 10-30% radiation dose reduction for equivalent effects among different tissues.

Antimetabolites

(456) 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-FU and capecitabine, and weak synergy with hydroxyurea and methotrexate (Hall and Giaccia, 2006).

Alkylating agents

(457) 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, others require activation by cytochrome p-450. The latter include alkyl sulfonates, ethyleneimines and methylmelamines, nitrogen mustards, nitrosoureas, triazines, imidazotetrazines, and platinum analogues. Strong synergy with radiotherapy effects in normal tissues has been noted with DTIC, intermediate synergy with platinum analogues, and weak synergy with BCNU and CCNU (Hall and Giaccia 2006).

Antiangiogenic drugs

(458) The recent use of antiangiogenic 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 anti-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).

Antibiotics and other agents

(459) 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 EGFR receptor dimerization and tyrosine kinase phosphorylation, which inhibits tyrosine kinase pathway signal transduction. However, EGFR inhibition was found not to alter the radiation response of oral mucosa in rodents to fractionated irradiation or 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 (Hall and Giaccia, 2006).

Recall reactions

(460) 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-FU, and interferon. Other non-cytotoxic agents such as simvastin, isoniazid, rifampicin, pyrazinamide and tamoxifen have also been implicated. Around 70 cases of recall have been reported since the first report in 1959 (Caloglu et al., 2007; Friedlander et al., 2004). Radiation is included in this list as another second agent demonstrating this phenomenon, where the mechanism is a dose-dependent incomplete recovery after the initial irradiation (Stewart, 2002).

3.2.9. Genetic and co-morbidity factors

(461) Several human genetic disorders are characterised by immune dysfunction and hypersensitivity to ionising radiation. Ataxia telangiectasia (*atm*), ataxia telangiectasia-like disorder, Nijmegen breakage syndrome, severe combined immune deficiency (*scid*), ligase IV syndrome, and Seckel syndrome are all disorders exhibiting a 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 (Bourguignon et al., 2005; Hecht and Hecht, 1990; ICRP, 1999).

(462) The proportion of individuals in the population that has high hypersensitivity (2 to 3- fold) is less than 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).

(463) 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 compared to patients in the remissive phase of these diseases (Cossu et al., 1991).

(464) AIDS patients exhibit higher radiotoxicity. Ionising radiation activates human immunodeficiency virus (HIV-1) replication, and bystander effects involving reactive oxygen species (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

(465) 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, hematopoietic growth factors (HGF) or colony stimulating factors (CSF), alone or in combination, have been evaluated in animal models, few have progressed successfully through clinical trials and approved for treatment of radiation-induced myelosuppression in humans.

(466) Treatment strategies for personnel exposed to acute, potentially lethal doses of radiation have been the subject of several international conferences during the past 20 years. Although a consensus for treatment was presented in a 1993 meeting (MacVittie et al. 1996) and in "Guidelines for Medical Management of the Acute Radiation Syndrome" (Waselenko et al. 2004), a U.S. 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 gathering of evidence needed to demonstrate efficacy against the lethal effects of radiation when efficacy studies in humans ethically cannot be conducted. 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. In this regard, it should be noted that even drugs such as G-CSF that are approved to treat chemotherapy-induced neutropenia are not approved to treat lethally irradiated personnel.

(467) 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 stmulate immune reconstitution in prophylactic and mitigation regimens respectively. The most important of these are described below.

(468) The translation of of treatment efficacy from relevant animal models to the human condition is less consistent. The FDA has approved four cytokines for the treatment chemotherapy-induced neutropenia and/or neutropenia consequent to myeoablative conditioning for stem cell transplantation. These are G-CSF, 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 so far.

Treatment for haematopoietic ARS consequent to terrorism or accidents

(469) Haematopoietic growth factors have been used in several cases of accidental exposures (Table 2.1). For example, in the Goiania accident in Brazil involving Cs-137, 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 during the past 15 years (Browne et al., 1990; Ricks et al., 2002; MacVittie et al., 1996; 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 The Strategic National Stockpile Radiation Working Group (Waselenko et al., 2004), the Centres for Disease Control and Prevention (CDC) has developed a protocol entitled “Neupogen for the treatment of ARS following a radiological incident”. In this protocol, individuals who have a history of exposure to radiation in the range 3-10 Gy, and who have a diagnosis of the haematopoietic syndrome as manifest by neutropenia (ANC ≤ 500/μL), would be treated with Filgrastim at 5 μg/kg/day subcutaneously (SC), in combination with medical management (intravenous fluids and antibiotics). Treatment should start as soon as possible after exposure and continue until ANC is > 1000/μL for 2-3 consecutive days. Treatment beyond 21-days could be extended if the ANC fails to reach >1,000/μl, or if the ANC, once above that threshold, drops below and remains at <1,000/μl for several days.

Treatment for haematopoietic myelosuppression in the clinic

(470) The number of patients receiving whole body radiation exposure and treatment with HGFs or cytokines is limited, 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 neutropenia (FN) exceeds 20% of the patient population. Three clinical studies in the early 1990’s 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 WBC 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 mobilization of CD34+ cells and “exhausted” the bone marrow capacity (Pape et al., 2006).

(471) The American Society of Clinical Oncology (ASCO) and the EORTC 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 (Smith, et al., 2006; Aapro et al., 2006). The U.S. committee extended their recommendations 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 recommended the use of G-CSF when a chemotherapy regimen is associated with FN in >20% of patients and in general recommended the use of CSFs and pegylated G-CSF to prevent FN and FN-related complications.

(472) The impact of the use of CSFs in children and the elderly has been the focus of several meta-analyses (Wittman et al., 2006; Sung et al., 2004; 2007), as well as a European Elderly Task Force (Repetto et al., 2003). These studies

show that primary prophylaxis with CSFs decreases the rates of infection, incidence of FN and duration of severe neutropenia.

(473) The CSFs, G-, GM- and pegylated G-CSF remain the only regulatory approved drugs available for the treatment of radiation-induced myelosuppression and potential lethal exposures within the haematopoietic ARS.

Experimental data on treatment of haematopoiesis suppression

Cytokines and growth factors

(474) Cytokines and GFs can enhance haematopoietic recovery after IR exposure. Animal studies have shown that IL-1, IL-3, IL-6, IL-11, macrophage-CSF (M-CSF), G-CSF, pegylated G-CSF, G-CSF mimetic (leridistem), pegylated leridistem, GM-CSF, TNF, c-kit L, FL, thrombopoietin (TPO), Megakaryocyte Growth and Development Factor (MGDF), vascular endothelial GF (VEGF) and several chimeric GFs containing two "linked" cytokines and a number of G-CSF peptide mimetics or G-CSF or TPO receptor agonists can stimulate haemopoiesis after irradiation (MacVittie and Farese 1995). The majority of cytokines and their inducers are most effective when initiated within the first 24 hours after irradiation, although cytokines such as IL-1 and TNF are also effective via prophylaxis. All of these HGFs demonstrated significant "potential" of moving from "bench to bedside" i.e. to be used 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, peg G-CSF, GM-CSF and IL-11 currently approved for treatment of respective lineage-specific myelosuppression.

(475) Activation of the nuclear factor–kB (NF–kB) 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 Flegellin*, is a Toll-like receptor 5 (TLR5) agonist, acting as an NF–kB-inducing agent that activates tumor-specific anti-apoptotic mechanisms. A single injection of CBLB502, given before lethal TBI, inhibited pro-apoptotic pathways and protected mice from gastrointestinal and hematopoietic ARS, resulting in improved survival. CBLB502 did not alleviate radiation-induced decreases in BM and blood cellularity but it did protect HSCs and early progenitors, as judged by preservation of granulocyte/macrophage colony-forming cells and stem cell populations in the BM. Additional studies in nonhuman primates were, however, statistically insignificant (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, TNFα) (Burdelya et al., 2008).

(476) 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 AR in the U.S. for approval to treat radiation-induced cellular damage in clinical protocols or lethally irradiated personnel consequent to a terrorist or accidental event.

Antioxidants

(477) The protective effects of antioxidants are mainly to be due to their scavenging ability of ROS (Prasad 2005; Tominaga et al., 2004). Antioxidants like ascorbic acid, phamitidin, melatonin and tempol also reduce radiation-induced apoptosis of lymphocytes (Mozdarani and Ghoraeian, 2008; Soule et al., 2007; Zhou et al., 2006). HPBLs (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 of radiation induced chromosomal damage *in vitro.* Antioxidants also activate enzymes involved in the repair of DNA lesions and decrease the activity of nitric oxide synthase, 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 the cellular and humoral immunity (Akleyev et al., 1995).

(478) 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 reactive oxygen species 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 regulating cell cycle, 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 HSC from radiation-induced oxidative stress and DNA damage. Additional studies demonstrate that the FoxO3 transcription factor represses ROS in HSC via regulation of ATM 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 HSC. 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 the p38 MAPK rescued defects in HSC repopulating ability and quiescence. Demonstration of the molecular mechanisms regulating HSC function and lifespan will be essential to developing new generation treatments for radiation effects in the haematopoietic sytem.

Stem cell therapy

(479) The number and quality of HSCs that survive irradiation are of critical importance for haemopoietic and immune recovery. A spontaneous recovery occurs if more than 2% of stem cells 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 haemopoietic cells (Fliedner et al., 2002). The feasibility of haemopoietic 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).

(480) Mesenchymal stem cells (MSCs) are non-haematopoietic, multipotent progenitor cells that are able to engraft at a very low level into the BM, 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 MSC include the stromal support for enhanced haematopoietic recovery after haematopoietic stem cell transplantation and the manipulation of immune responses (Le Blanc, 2003).

(481) 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 HSC or the GI 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 is low and there are large interspecies differences.

Experimental data on treatment of immunosuppression

(482) Post-irradiation 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, 2009; 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 (ETP) and their continued seeding of a competent thymus (Bhandoola and Sambandam, 2006). Since there are no effective treatments currently approved for clinical use, new strategies are required to promote thymic-dependent T cell regeneration. The thymic microenviroment offers another target for treatment of immune suppression. The ability to enhance seeding of ETP and/or T cell regeneration within the niche may be of marked benefit. The thymic epithelial cells (TEC) are constantly renewing themselves while maintaining a steady-state ratio within the thymocyte subsets and are likely amenable to regulation by exogenous GFs (Gray et al., 2006). The nature and extent of post-radiation immunodeficiency can be modified by antioxidants, cytokines and growth factors, which can stimulate immune regeneration via effects on bone marrow–derived HSC and/or ETP, as well as stimulating recovery and function within the thymic niche (Rossi et al., 2007). Several cytrokines and immunomodulators such as IL-1, IL-2, IL-4, IL-7, IL-15, IL-17, c-kit Ligand (KL), Flt-3 Ligand (FL) thymic stromal lymphopoietic

(TSLP), bone morphogenetic proteins (BMP) and fibroblast GF (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

(483) 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 TEC in both the cortical and medullary regions. The KGF (FGF-7) receptor is expressed on TEC and in turn, TEC 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 TEC (Chung et al., 2001). The literature documents treatment efficacy of prophylactic administration of KGF in various models of murine bone marrow transplant (BMT). KGF pretreatment increased thymopoietic capacity of mice after congenic or allogenic BMT and after various conditioning regimens (6.5 Gy to 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 post-BMT thymopoiesis and immune recovery.

(484) IL-7 is produced by a subset of TEC and bone marrow cells and is a stimulus for proliferation, survival and differentiation of immature thymocytes (Fry et al 2005). IL-7 treatment of irradiated mice resulted in preferential expansion of CD8+ T cells and more rapid normalization of the CD4/CD8 ratio. Additional studies showed that mice treated with IL-7 post 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 SIV-infected macaques increased both CD4+ and CD8+ T cells and enhanced homeostic peripheral expansion (HPE) (Fry et al., 2003; Moniuszko et al., 2004).

(485) FL, while not in clinical trials for treatment of radiation or chemotherapy-induced immunosuppression, is an essential component of *in situ* physiologic regulation of haematopoietic and lymphoid development, as well as a functional immune response in lymphopenic hosts. FL utilization 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; Kennis et al., 2008). Furthermore, FL 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 HPE.

Antioxidants

(486) Antioxidants exert a stimulating effect on innate immunity following irradiation in a wide range of doses. Glutathione (GSH) and its precursors, such as cysteine and N-acetylcysteine, activate both lymphocytes and NK cells after low dose whole body γ-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). Metalothionine-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 γ-radiation (7-9 Gy) (Matsubara et al., 2000).

(487) 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 (LAK) cells, and production of several cytokines (such as IL-1, IL-6, IFN-γ and IL-12) required for hematopoietic recovery. Ginsan was shown to enhance Th1 function while interfering with the radiation-induced Th2 response (UNSCEAR, 2009).

Other experimental approached for stimulated immune recovery

(488) Animal studies have shown that immunisation and vaccination can significantly modify post-exposure 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; Shankar et al., 1999).

(489) Vaccines can also stimulate the phagocytic activity of neutrophils and bactericidal blood serum properties of irradiated experimental animals (Chertkov, 2004). Antitularemic and antituberculosis BCG vaccines decrease chromosome aberrations in bone marrow cells at early times after irradiation (Andrushchenko et al., 1996).

(490) Microbic cell components (polysaccharides and lipopolysaccharides) can also exert post-irradiation immunostimulating 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 a 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 substantially increase RBM regeneration after irradiation (Patchen et al., 1989). Similarly, glycolipid trehalose dimycolate can increase host defense mechanisms against a variety of microorganisms, and of increasing survival after TBI (Giambarresi and Walker, 1989).

3.3.2. Digestive system

(491) Our understanding of the complex pathogenetic mechanisms that lead to development of radiation-induced bowel injury has improved considerably during the last 20-30 years. Hence, extensive pre-clinical 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; Feyer et al., 2005; Keefe et al., 2007; Maranzano et al., 2005; Rubenstein et al., 2004).

(492) Prophylactic interventions aimed at ameliorating normal tissue radiation injury fall in two conceptually different categories: 1) strategies that interfere with radiation-specific mechanisms of injury, for example, antioxidants, free radical scavengers and other cytoprotective agents; and 2) 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

(493) 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).

(494) The free radical scavenger amifostine protects both small and large intestine in pre-clinical studies (Carroll et al., 1995; Ito et al., 1986), and clinical studies also suggest that amifostine protects against gastrointestinal radiation toxicity (Athanassious 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 intra-rectal instillation of amifostine, 30 minutes 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.

(495) 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 (Caroll et al., 1995; Rowe et al., 1993); tirizalad and other peroxidation inhibitors (Bonsack et al., 1999; Delaney et al., 1992; Felemovicius et al., 1998); as well as vitamin A and vitamin E (Beyzadeoglu et al., 1997; Caroll et al., 19951; Felemovicius et al., 1995).

Prostaglandins

(496) Prostaglandins or other modifiers of cyclooxygenase 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. Prostaglandin E2, enprostil (a prostaglandin E2 analogue), and misoprostol (a prostaglandin E1 analogue) protect against intestinal radiation toxicity in animal models (Delaney et al., 1994b; Hanson and Thomas 1983; Keelan et al., 1992; Tomas-de la Vega et al., 1984). 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

(497) 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.

(498) Among the interleukins (IL), preclinical evidence suggests a protective effect of IL-1 (Hancock et al., 1991; Wu and Miyamoto, 1990), IL-7 (Welniak et al., 2001), and IL-11 (Orazi et al., 1996; Potten, 1995; 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).

(499) Angiogenic growth factors, e.g. acidic fibroblast growth factor (aFGF, FGF-1); basic fibroblast growth factor (bFGF, FGF-2); and vascular endothelial growth factor (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.

(500) 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 (Farrell et al., 1998; Khan et al., 1997). 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.

(501) Transforming growth factor beta 1 (TGF-β1) 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-β1 in radiation fibrosis in many organs, including the intestine. A preclinical study demonstrated a direct mechanistic role for TGF-β1 in intestinal radiation fibrosis, as well as the potential for anti-TGF-β1 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 signaling (Boerma et al., 2008b).

(502) Evidence from preclinical studies suggests that other cytokines may be considered as intestinal radiation response modifiers. Hence, stem cell factor (SCF), mast cell growth factor, c-Kit ligand), growth hormone (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 (Arango et al., 2001; Howarth et al., 1997; Leigh et al., 1995; Silver et al., 1999; Vazquez et al., 1999). The potential of these mediators as modifiers of the intestinal radiation response in the clinical situation is still unknown.

Enterotrophic strategies

(503) There has been long-standing interest in the use of enterotrophic strategies (i.e. interventions that promote growth of the intestinal mucosa) to

ameliorate 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.

(504) Elemental diets are enteroprotective in animal studies, but results from clinical trials are mixed (Brown et al., 1980; Craighead and Young, 1998 /4189; Douglass et al., 1978; Foster et al., 1980; McArdle et al., 1986). 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.

(505) 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 supports mucosal structure and recovery and ameliorates intestinal radiation toxicity in some preclinical studies (Campos et al., 1996; Klimberg et al., 1990), although not in others (Hwang et al., 2003; McArdle 1994). 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).

(506) Numerous gastrointestinal peptide hormones have potent enterotrophic activities. This category includes growth hormone, 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

(507) Even though 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 (ASA, aspirin), an anti-inflammatory agent with antiplatelet properties, may be of some benefit in intestinal radiation toxicity (Mennie et al., 1975), whereas, other nonsteroidal anti-inflammatories (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 therapy of inflammatory bowel disease are not only ineffective, but possibly even harmful when used in the prophylaxis of acute intestinal radiation toxicity (Baughan et al., 1993; Freund et al., 1987; 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 to specific aspects of the inflammatory process, may prove more effective in modifying the intestinal radiation response.

Modulation of intraluminal contents

(508) 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).

(509) 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 (Hauer-Jensen et al., 1985; Morgenstern et al., 1970; Rachootin et al., 1972; Sokol et al., 1967). 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 antiangiogenic effects (Patel et al., 1994; Weckbecker et al., 1992a,b; 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

(510) Administration of traditional anticoagulant agents, such as heparin, warfarin, or acetyl salicylic 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., 2002; 2004). Strategies aimed at restoring local endothelial anticoagulant properties, temporarily replacing the "natural anticoagulant", activated protein C, or blocking only the effects of thrombin that are mediated through its cellular receptor, proteinase-activated receptor 1 (PAR-1), are under investigation.

(511) 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, also the acute intestinal radiation response (Haydont et al., 2007; Wang et al., 2007).

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, for example the vitamin E analogue, γ-tocotrienol, can further enhance the efficacy of statins as effective radiation response modifiers.

Neuro-immunomodulation

(512) 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 only as conveyors of stimuli from the periphery to the central nervous system or peripheral neural circuitry. However, it is now well established that sensory nerves also exert important local effector functions in many organs, particularly in 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 (NK-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 both 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 (CGRP) ameliorates, the intestinal radiation response (Wang et al., 2006 a, b; Zheng et al., 2000).

Pre-exposure countermeasures after radiation accidents or radiation terrorism

(513) 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 cleanup 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 total 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.

(514) 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., 2002). Tocols have been subject to particular interest because of their potent properties as radiation

protectors. The 8 naturally occurring tocols (α, β, γ, and δ tocopherols and 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 factor around 1.3, protecting against hematopoietic 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.

(515) Several small molecule compounds that mimic the effects of SOD and/or catalase are under development as radioprotectors and have shown shown promise as countermeasures, but their ability to specifically protect from intestinal radiation lethality after total body irradiation remains to be determined (Kumar et al., 1988; Rong et al., 1999; Vujaskovic et al., 2002a).

(516) 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 total body irradiation 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 (Monobe et al., 2005; Vijayalaxmi et al., 1999).

(517) Many studies have assessed modification of cyclo-oxygenase (COX) activity or components of the arachidonic acid cascade in the context of radiation responses in normal tissues, including intestine. Inhibition of COX2 protects against intestinal radiation injury in animal studies, (Keskek et al., 2006), as do prostaglandin E (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 (Delaney et al., 1994; Keelan et al., 1992b). 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).

(518) Several GF, and chemokines have been shown to reduce intestinal injury after total body irradiation. For example, IL1α IL1β, Teduglutide , TGF-β3, IL11, genistein, confer some radioprotection of mouse intestine (Hancock et al., 1991; Potten, 1995; Potten et al 1997; Wu and Miyamoto, 1990). Interleukin 7 (IL7), 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 intraepithelial lymphocytes (IELs) from undergoing apoptosis (Yada et al., 2001). It may also protect the intestinal stem cell compartment from radiation (Welniak et al., 2001). Interleukin 15 (IL15), a cytokine that is widely expressed by epithelial cells, stromal cells, and immune cells, promotes survival of IELs, inhibits expression of interleukin 8 (IL8) and monocyte chemoattractant protein 1 (MCP1) (Lai et al., 1999; Lugering et al., 1999), and stimulates epithelial cell proliferation (Reinecker et al., 1996).

While IL15 has not been systematically studied 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 GI toxicity, mainly due to dose-limiting diarrhoea (Cao et al., 1998).

(519) The angiogenic growth factors, aFGF, bFGF, and VEGF, are all radioprotective in the small intestine of mice exposed to total-body irradiation (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.

(520) Direct enterotrophic growth factors, for example recombinant human KGF1, administered to mice before total-body or abdominal irradiation increased crypt survival and LD50 (Farrell et al., 1998; Khan et al., 1997).

Post-exposure countermeasures against intestinal radiation injury

(521) Post-exposure 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 to 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.

(522) Modifications of the intraluminal contents, particularly bacteria and pancreatic enzymes, have been explored as strategies to ameliorate intestinal radiation toxicity in the post-exposure 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 total body irradiation situation and should be avoided. Careful selection of antibiotic treatment regimen has been shown to protect lethally irradiated canines (Kumar et al., 2002). A combination of oral and parenteral antibiotics may reduce bacterial translocation and confer considerable protection. In the clinical situation, it is likely that the 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).

(523) 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 et al., 1970; Morgenstern and Hiatt, 1967; Rachootin et al., 1972; Sokol et al., 1967). The most promising approach to reduce intraluminal pancreatic secretions in humans may be by administration of synthetic somatostatin receptor analogues. Somatostatin analogs are “universal gastrointestinal inhibitors” and used clinically for a wide variety of gastroenterological indications. Because of 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 localized irradiation, there is interest in developing somatostatin analogues for use as countermeasures as well (Fu et al., 2009).

(524) The polypeptide compound, CBLB502, derived from Salmonella flagellin, binds to Toll-like receptor 5 (TLR5) to activate signalling by nuclear factor κB (NFκB). Activation of NFκB 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 total body irradiation in mice and non-human primates. CBLB502 improves survival both when injected up to 24 hours before radiation exposure, as well as when injected up to 1 hour after radiation exposure (Burdelya et al., 2008).

(525) Interleukin 11 (IL11), in addition to its haematopoietic and immunomodulating activities, also serves to protect and restore the GI mucosa. Administration of IL11 protects mice against the intestinal effects of total-body irradiation (Orazi et al., 1996; Potten, 1995; 1996). Despite these encouraging preclinical results, systemic administration of IL11 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 IL11 (rhIL11) avoids systemic uptake and is thus not associated with the toxicity seen after systemic administration (Cotreau et al., 2004; Tseng et al., 2000). A recent study showed significant protection against early intestinal radiation injury when human recombinant IL11 was administered once-daily directly into the intestinal lumen of rats (Boerma et al., 2007), suggesting that oral administration of an enterosoluble form of IL11 may also be a promising radiation countermeasure.

3.3.3. Reproductive system

(526) 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

(527) Suppression of gonadotropins with medroxyprogesterone acetate during chemotherapy combined with radiotherapy did not improve the recovery of sperm counts or normalize 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 antiandrogen (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 leukemia 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.

(528) 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 estradiol 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 (Boekelheide et al., 2005; Kamischke et al., 2003). Meistrich and colleagues 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 (Meistrich et al., 2000). In rats, radiation produced a prolonged block to spermatogonial differentiation (Meistrich et al., 1999).

(529) Control rats and rats treated with testosterone plus estradiol 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 weights, sperm counts and the tubule repopulation indices. Greater recovery of spermatogenesis was observed for all endpoints, with a DMF of about 2 for rats treated with testosterone plus estradiol compared to the irradiated, cholesterol-treated rats. The DMF values were similar for both neutrons and in previous studies using γ-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.

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 Posttreatment 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 posttreatment 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 posttreatment 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 protected spermatogenesis from damage by cyclophosphamide (one study) Delayed posttreatment suppression failed to restore spermatogenesis	Several non-randomized studies (some with concurrent controls) indicate that suppression markedly protects against premature ovarian failure One small randomized study showed no protective effect of suppression

(530) 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-labeling of DNA fragmentation 16 h after irradiation (Otala et al., 2004). However, the numbers of primary spermatocytes and spermatogonia at G2 were higher after 21 days in the SIP-treated testes compared with vehicle-treated testes, indicating protection of early spermatogonia by S1P, whereas the spermatid populations were similar. The authors concluded that S1P appeared to protect partially (16-47 %) testicular germ cells against radiation-induced cell death.

Antioxidants

(531) 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, H^{125}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 H^{125}IPDM. The dose modification factors (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 H^{125}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.

(532) RP-1, a herbal preparation of Podophyllum hexandrum, already reported to provide protection against whole body lethal γ-irradiation (10 Gy), was studied regarding radioprotection of spermatogenesis in mice (Samanta et al., 2004; Samanta and Goel, 2002). 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 counts and reduction in abnormalities of sperm morphology, at 10, 35 and 70 days after irradiation. Testis thiol content was found to be increased in both RP-1 alone and RP-1-pre-treated 10 Gy-irradiated groups compared to the 10 Gy-alone groups at 8, 16 and 24 h. Irradiation (10 Gy) significantly decreased glutathione peroxidase, S-transferase and reductase activity in comparison to 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 to 10 Gy-alone, 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

(533) The radioprotection of testicular cells using amifostine and doses of radiation extending down to less than 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 (PF) obtained by injection of 400 mg/kg WR-2721 at 15 min prior to irradiation decreased from about 1.4 at radiation doses above 10 Gy to 1.0 at 2 Gy. Similarly, the radioprotection by 300 mg/kg WR-2721 was reduced from a PF of about 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 5 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 due, at least in part, to a direct cytotoxic effect of WR-2721 on testicular stem cells. Protection of differentiated spermatogonia was observed with 400 mg/kg WR-2721; the PF 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 to the protection of stem cell survival. At 8 Gy the PF with 400 mg/kg WR-2721 for both functional endpoints was about 1.5, which was not significantly different from the value of 1.3 obtained using the stem cell assays.

(534) A study was made of the protective effect of some radioprotective agents against dominant lethal mutations (DLM) in post-spermatogonial stages and reciprocal translocations (RT) induced by γ-radiation in spermatogonia of mice (Pomerantseva and Ramaija 1984). Among the radioprotective agents used, cystaphos, a combination of cystamine and 5-MOT and a mixture of 6 components proved to be most effective against DLM, and cystaphos, gammaphos and cystamine combined with 5-MOT proved effective against RT. The degree of radioprotective efficacy was relatively low. The efficacy of cystamine in protecting against RT was higher with exposure of gonocytes of

18.5-day embryos than spermatogonia of pubertal animals. The degree of 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 ionizing radiation.

(535) 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. Iodine-125 was localised in either the cytoplasm ($H^{125}IPDM$) or in the DNA ($^{125}IUdR$) 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 dose modification factors (DMF) 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.

(536) 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 +/- 1 %) caused by irradiation (5 Gy) was also reduced to 8 +/- 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

(537) 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 might be protective of ovarian function, none of the studies was prospectively randomised and thus the results are inconclusive.

(538) 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).

(539) The use of sphingosine 1-phosphate (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

(540) Three-week-old female mice, with or without pretreatment with amifostine, were irradiated with 6.4 Gy γ-rays (Yoon et al., 2005). The incidence of follicular degeneration increased in ovarian follicles in the γ-irradiated mice compared to that of the control or amifostine-treated group. There was a rise of p53 and Bax protein and a decline of the inactive form in caspase-3 and PARP 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 γ-rays, affecting the expression of apoptotic signaling molecules and the level of proliferation of the granulosa cells.

(541) There was also an early report of protection of ovarian follicles in mice by MPG (2-mercaptopropionylglycine) (Kumar and Uma Devi, 1983).

3.3.4. Skin

Anti-inflammatory agents

(542) 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 nonsteroidal anti-inflammatory drugs are of value in the prefibrotic 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 remained unproven (Delainian et al., 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 non-steroidal anti-inflammatory agent trimetazidine, when given with flurbiprofen, reduced moist dequamation after irradiation in rabbit skin, but not when given alone (Lefaix et al., 1992).

Superoxide dismutase

(543) 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 Delainian et al., 2007)). However, as yet, SOD and its various preparations are not available for general clinical use.

Pentoxifylline (PTX)

(544) PTX was reported to significantly accelerate healing of radiotherapy-induced soft-tissue necrosis (Dion et al., 1990). Also, in a Phase II Trial there was complete restoration of refractory mandibular osteoradionecrosis by prolonged treatment with a pentoxifylline-tocopherol-clodronate combination (PENTOCLO) (Delanian et al., 2010). In animals, PTX was found not 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-Tochopherol (vitamin E)

(545) In a randomised trial of breast cancer patients with skin fibrosis, regression of of the fibrotic lesions was observed after administration of PTX/tocopherol (Delanian et al., 2003). However, these results were not confirmed in larger trials in breast cancer patients (Gothard et al., 2004) and in patients after pelvic radiotherapy (Gothard et al., 2005). Tochopherol in combination with pentoxifylline (PTX) 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 tochopherol on its own in rabbits (Lefaix et al., 1992). Pig skin was also used as a model to study the effectiveness of two topically applied creams post-irradiation, Lipochromin (containing β carotene, tochopherol, fatty acids) and Levosinum (containing methyluracil, sulfadimethoxin) in modifying the development of both early and late radiation (^{90}Sr/^{90}Y beta-rays) damage. Application of Levosinum shortened the healing time of moist desquamation at each of 4 dose levels by 5-10 days. In 3 out of 4 dose levels used, this shortening of the healing time was statistically significant ($p < 0.03$). Treatment with these topical applications also reduced the incidence of late dermal necrosis and increased the ED50 values for the incidence of dermal necrosis, equivalent to a dose modification factor of 1.11-1.13 (Rezvani et al., 2000).

Growth factors

(546) Esculentoside A was reported to protect soft tissues against radiation toxicity through inhibiting the production of several proinflammatory 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 a downregulation of both inflammatory and fibrogenic cytokines in irradiated skin and muscle, particularly in the early phase after irradiation (Okunieff et al., 2006). TGF-beta 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 post-irradiation (25 Gy) impaired cutaneous wound-healing model in rats (Tattini et al., 2008).

ACE inhibitors

(547) 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 it reduced the incidence of dermal necrosis (Ward et al., 1990).

Essential fatty acids

(548) Essential fatty acids were administered orally to pigs after skin irradiation ($^{90}Sr/^{90}Y$ 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. Dose modification factors were between 1.06-1.24 for the acute reactions of bright red erythema and/or moist desquamation, and of 1.14-1.35 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 dose modification factors of between 1.13-1.24 for acute reactions, and 1.14-1.51 for late erythema or dermal necrosis (Hopewell et al., 1993). Daily evening primrose oil dietary supplementation 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

(549) Amifostine has been reported to protect against skin reactions from radiotherapy (reviewed by Santini, 2001). Mercaptoethylamine (MEA), dimethylsulfoxide (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 MEA giving the most protection and DMSO the least (Moulder et al., 1977). Low doses of amifostine (0.2-0.3 mg/g) were also used before each of 1, 5 or 10 fractions given to mouse skin. The degree of protection was similar in all three systems and it did not change significantly with fractionation (Rojas et al., 1986). Systemic or topical 16-16 dm PGE_2 protected against single dose radiation-induced hair loss (Hanson et al., 1992), and PGE_2 or amifostine protected against fractionated radiation doses (Geng et al., 1992 /5686)). Three weeks after systemic administration of 16-16 dm PGE_2 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 to irradiated-only skin sites. The thiol compound effects were slightly superior to the PG effects in these studies. Local applications of 16-16 dm PGE_2 or WR-1065 given 15 min before each radiation fraction also enhanced post-radiation hair regrowth, although systemic administration of either agent was more effective than the topical route (Malkinson et al., 1993).

Nitroxides

(550) A clinical study demonstrated that topical application of Tempol to the scalp before whole brain radiation was safe, 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 to 11 postirradiation hair loss was much reduced in nitroxide-treated animals compared to in controls (Cuscela et al., 1996).

Adriamycin

(551) Adriamycin has been shown to enhance skin reactions in patients who are receiving or who have received radiation therapy (Cassady et al., 1975; Donaldson et al., 1974). 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

(552) 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

(553) 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, dose-modifying factors have been reported of 1.6-2.2 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 dose modifying factors up to 1.3 have been reported. The hypoxia also could be reduced by warming the skin or by using pentobarbitol anaesthetics.

(554) It has also been noted in case reports that hyperbaric oxygen treatment given after irradiation has shown some benefit in improving wound healing in irradiated skin (reviewed by Olascoaga et al., 2008). However, another review concluded that HBO did not appear to be an effective treatment for radiation-induced fibrosis (Delainian, 2007).

Genetic variability in response

(555) Reactions in skin after irradiation are, like those in other tissues, dependent on the genetic profile of the individual. The classical example is ataxia telangiectasia (ATM), which is an autosomal recessive disease affecting 1 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

ataxia telangiectasia 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 et al. 1993; Morris and Powell 1997; Chen et al., 2001; Phan et al., 2003).

(556) The incidence of late radiation-induced skin telangiectasia is also known to vary among 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

(557) Lack of full recovery in tissues after a first irradiation may cause a more severe response to a second treatment. In man, 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). In mouse skin there is 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; Simmonds et al., 1989; Terry et al., 1989; Wondergem and Haveman, 1987). For radiation-induced necrosis of the mouse tail skin, the tolerance dose was reduced by about 10% at times greater than 6 weeks after a first 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

(558) 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 for instance using ACE inhibitors such as

enalapril and captopril (Wouters et al., 2005; Yeh et al., 2004). 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 to develop congestive heart failure were randomised to receive or not to 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

(559) In a rat study 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 the clinical studies are sparse.

Pentoxifylline

(560) PTX inhibits fibroblast proliferation and has also been shown to inhibit intracellular signaling in response to TGFβ and CTGF. Two experimental studies have shown that that PTX 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; Lui et al., 2009). The subsequent withdrawal of drugs was, however, associated with a rebound effect, with development of fibrosis.

Stem cell replacement

(561) 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 haematopoietic stem cells, 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)

(562) 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 that can both 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 adult unconditioned mice, human mesenchymal stem cells migrated in bone marrow but also into other tissues. Total body irradiation increased human mesenchymal stem cells implantation in bone marrow and muscle and further led to engraftment in brain, heart and liver (Mouiseddine et al., 2007). There is no experience in humans yet with the use of human mesenchymal stem cells to repair radiation induced cardiac damage.

Anthracyclines

(563) 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 below 500 mg/m^2 are usually well tolerated (Kremer et al., 2001; Steinherz 1997). 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 defenses. 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 by two to three-fold compared to radiotherapy alone (Aleman et al., 2007; Moser et al., 2006); this effect may also be more than additive (Myrehaug et al., 2008)

Taxanes

(564) Taxanes are now 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

(565) 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. Further studies are however needed to define its role in radiation-induced toxicity (Savarese et al., 2003).

Biologicals

(566) 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 tumor tissue, but also on cardiomyocytes, where it exerts a protective effect on cardiac function. Interference with ErbB2-signaling 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 or to be associated with ultrastructural changes in the myocardium and seems 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. Belkacémi performed a study in 146 breast cancer patients treated with adjuvant trastuzumab and radiotherapy concomitantly. In this study, 103 patients were irradiated on the internal mammary nodes. They observed significantly more acute left ventricle ejection fraction decreases in 146 patients using weekly trastuzumab compared to the administration every 3 weeks. (Belkacemi et al., 2008). 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

(567) Since the first reports of ocular effects of ionising radiation exposure in cyclotron workers(Abelsons et al.,1949) and A-bomb survivors (Cogan et al., 1949), there has been a considerable effort to test and develop pharmacologic 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

(568) Within two years after the first reports of radiation cataract in cyclotron workers and victims of the atomic bombings, von Sallman 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 Sallman et al., 1951; von Sallman, 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 expanded on this observation and provided an alternative and mechanistic explanation for their 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 (Piri,1959).

(569) 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 dimercaprol 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 rather gross changes in lens structure and clarity, rather than slit lamp examination, more often utilised in later reports.

(570) Francois also reported partial protection of the lens by intravenous pretreatment of rats with 2-mercaptoethylamine (Francois and Beheyt,1955). 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 reported that swelling of the lens sutures, an early hallmark of radiation exposure 24-48 hrs following exposure, was reduced by occular injection of glutathione, 15 min prior to irradiation of the rabbit head with 8-60 Gy (Swanson et al., 1957). Ocular pathology was only monitored for 48 hrs 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 also noted protection of a variety of ocular structures by cysteine pretreatment prior to exposure of rabbit eyes to 10-20 Gy (Straub and Krause, 1958). Conjunctivitis, epilation and subsequent cataract formation were reduced by i.v. injection of cysteine up to 2 hours prior to irradiation.

(571) A limited study of the effects of cysteine on the cornea, but not any other eye structures, revealed that i.p. injection prevented some X-ray damage but retrobulbar local injection did not (Blodi, 1960).

(572) In subsequent years, more powerful radioprotective sulfhydryl compounds were tested, such as AET (2-aminoethylisothiouronium bromide) (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 also tested AET for radioprotection against X-ray induced cataract-associated changes in guinea pigs following exposure to 4 or 10 Gy. I.p. injection of 150 mg/kg led to a significant reduction in ^{32}P uptake (as a proxy for mitotic activity) for up to 96 hours following exposure, as compared irradiated but untreated guinea pigs (Ismail et al., 1971).

(573) 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

(574) 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 (1,160 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 intraocular drug concentrations were achieved 15-60 minutes after i.p. injection (Osgood et al., 1986). Curiously, the highest intraocular levels were found in choroid and retina and the lowest 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 that of the avascular lens fiber cell mass. Nevertheless, the fairly high concentration,

administered within 30 minutes of irradiation, raises questions about the clinical relevance of such phosphorothioate compounds in humans.

(575) A later report from the same group (Livesey et al., 1995) indicated 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 drug 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 30-120 minutes before irradiation; treatment more than 24 hours before or 30 minutes or later following exposure to 15.3 Gy of ^{137}Cs was ineffective in preventing cataract formation.

(576) Similar findings were reported using 500 mg/kg Amifostine (WR 2721) administered 30 minutes 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 1,160 mg/kg WR-77913 in preventing lens fiber cell swelling and disruption of the bow region. 250 mg/kg WR-2721, however, 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*.

(577) The rapid clearance of WR compounds and their relatively low toxicity compared to other sulfhydryl agents, suggest 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).

(578) The precise mechanisms by which WR-77913 or WR2721 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 and Droy-Lefaix, 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 (Clark and Steele, 1992; Roberts et al., 1991).

Metalloporphyrins

(579) 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 one hour after direct intraocular 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 to 0% in the MnTMPyP treated group. Approximately 25% of these treated animals exhibited a 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 to untreated, irradiated animals. Similarly, the retinal microvasculature was almost completely preserved in treated animals irradiated with 28 Gy compared to extensive vascular damage in untreated irradiated retinas. 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

(580) 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-ray (Sasaki et al., 1998). Tempol was injected into the anterior chamber 15 minutes 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.

(581) Carnitine, and its metabolites, is reported to have anti-oxidant 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 anti-cataract agent. To test this, rats were exposed to a single dose of 5 Gy ^{60}Co with or without L-carnitine (100 mg/kg i.p., 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 (MDA) 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, which has been suggested to protect the lens from osmotic stress in an animal model of diabetic cataract formation (Pessoto et al., 1997).

(582) Recent work suggests that 200 mg/kg/day carnitine, or 40 mg/kg/day vitamin E 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 ^{60}Co. It should be noted that, in comparison to radiation-induced lens pathology, much higher doses of radiation are required to damage retinal tissue.

(583) Other studies (Karslioglu et al., 2004) showed that pretreatment of rats with 10 mg/kg/day vitamin E reduced the radiation cataract grade, inhibited radiation-induced elevation in lens MDA, and inhibited elevation of GSH-PX and SOD. However, the failure to follow animals for more than 10 days following exposure is a significant concern regarding the long-term efficacy of vitamin E in preventing radiation cataract.

(584) 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 Dray-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.

(585) 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 MDA 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 be an early or initiating factor (Orhan et al., 1999).

Oestrogen

(586) A series of recent papers has reported both negative and positive radioprotective effects of oestrogen in ^{60}Co gamma irradiated rat eyes. Estradiol given to ovariectomised female rats prior to irradiation increased both the rate and incidence of lens opacities (Dynlacht et al., 2006). In contrast, the same compound administered post-irradiation, via subcutaneous slow release, had significant protective effects (Dynlacht et al., 2008). Further studies demonstrated that the oestrogen effect was limited to females, as male rats implanted with 17-β-estradiol showed no difference in radiation cataract incidence after exposure to 10 Gy ^{60}Co (Henderson et al., 2009). Male rats had a significantly greater incidence of PSC than females when animals were followed for up to 500 days post-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 radiation cataract incidence.

(587) In contrast to the findings with low-LET exposure, male rats implanted with 17-β-estradiol and exposed to 1 Gy high-LET ^{56}Fe ions exhibited greater incidence and rate of progression of lens opacities compared to 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

(588) 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-ray, 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

(589) Topical ocular pre-treatment with 10% DMSO in mice was effective in preventing total lens opacification after whole head irradiation with 10 Gy X-ray (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.

(590) 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.

(591) In contrast to reported lens protection, topical administration of 10% DMSO resulted in corneal radiosensitisation in mice (Hagemann etal., 1970). Corneal lesions were observed in 50-80% of treated mice but not in irradiated controls. The apparent corneal radiosensitisation suggests DMSO and related compounds may have limited usefulness in limiting eye radiation effects.

Bowman-Birk Inhibitor Concentrate (BBIC)

(592) Mice fed BBIC, a protease inhibitor, in their diet before and after exposure to 50 cGy ^{56}Fe HZE 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 300 cGy 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 (NAC), 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

(593) 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 one week prior or as much as one week after irradiation with 11 Gy. This is surprising, since sugars are believed to exert their

radioprotective effect by scavenging short-lived free radicals formed during irradiation.

3.3.7. Respiratory system

Antioxidants

(594) 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 infiltraton and TGFβ 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 TGFβ activation and downregulation of the profibrotic TGFβ–Smad3 signaling 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 irradiaton.

(595) Another experimental rat model demonstrated that both MnSOD and CuZnSOD were effective at reducing micronucleus formation in fibroblasts when given 30 minutes before or immediately after whole 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 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

(596) 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 iradiation 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 TGFβ levels in plasma 1-3 months after thoracic irradiation and reduced the accumulation of macrophages and expression and activation of TGFβ in irradiated lung tissue at 6 months after irradiation (Vujaskovic et al.,

2002b). In those studies where dose response relationships were investigated, protection factors (PF) for lethal pneumonitis at <9 months after irradiation in air were in the range 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 greater, in the range 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).

(597) There is also evidence for radioprotection of lung tissue in some clinical trials, although 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% verus 43% grade 2 pneumonitis; 28% versus 53% fibrosis at 6 months). The amifostine was generally well tolerated but 7% patients developed transient hypotension. Two subsequent randomised trials demonstrated protective efects 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 chemo-radiotherapy. 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).

Antiinflammatory and anticoagulant agents

(598) There is abundant pre-clinical evidence to show that chronic administration of steroidal anti-inflammatory drugs can decrease the acute inflammatory response in irradiated rodent lungs (reviewed in 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 to 50%) (Gross 1980; Gross et al., 1988 /5878; Phillips et al., 1975). 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 cyclooxygenase, e.g. aspirin, or the lipoxgenase pathway, e.g. diethylcarbamazine, have been shown to protect against lethal radiation pneumonitis, although other cyclooxygenase inhibitors, like 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.

(599) 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 hypercholesterolemia 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 pneumnitis, 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).

(600) Pentoxifylline is an antithrombotic drug that inhibits platelet aggregation by stimulating the release of prostacyclin and inhibition of phospholipase A2 and TNFα 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 dysfynction or acute lung injury was seen (Koh et al., 1995; Ward et al., 1992). 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 both from objective LENT-SOMA scores and functional perfusion scans (Ozturk et al., 2004).

ACE inhibitors and AII receptor antagonists

(601) Ward and colleagues 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., 1990), 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 the captopril for beneficial effects; rapid deterioration of lung density was seen if the drug was withdrawn from the rats at 3 months after irradiation (reported in 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 (Moulder et al., 1998; Ward et al., 1989). 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 AT receptors is involved in the development of radiation pneumonitis.

(602) Despite the encouraging pre-clinical 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

(603) Numerous studies have demonstrated TGFβ 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 TGFβ activation and thereby ameliorate damage in the irradiated lung. Recombinant human adenoviral vector carrying the soluble TGFβ 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 TGFβ (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 (Nishioka et al., 2004; Rabbani et al., 2003).

(604) 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-TGFβ antibody, given immediately after fractionated irradiation to the right lung, reduced the macrophage accumulation, TGFβ activity and alveolar thicknes at 6 weeks after irradiation. At 6 months after irradiation, there was a significant reduction in ,TGFβ activation and downstream target proteins Smad3 and phosphorylated Smad2/3, as well as reduced collagen deposition, in lungs of the antibody treated rats. These results suggest that the neutralising antibody acts at the tissue level to decrease the availability of TGFβ. Similar protective effects were seen when a small molecule TGFβ type 1 receptor kinase inhibitor was given continuously in the chow, from 1 week before irradiation (Anscher et al., 2008). Drug treated rats had less histological lung damage, less breathing difficulties, less oxidative stress and TGFβ expression in the lung tissue and less lung fibrosis than rats given the control chow. Drug treatment for only 3 weeks after irradiation was less effective than continuous drug administration.

(605) 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 TGFβ expression in experimental models of bleomycin and acute radiation induced lung injury (Chen et al., 2004; Yi et al., 1996; 1998). 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 αvβ6 and TGFβ 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 TGFβ activation and late fibrosis.

(606) 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

Antiinflammatory agents

(607) High dose steroids given together with fractionated renal irradiation increased the severity of glomerular and vascular lesions in rats (Berdjis, 1960) and decreased survival time in rabbits (Caldwell, 1971). However, later studies using chronic low dose administration of dexamethasone demonstrated a delay 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 captoril 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).

(608) 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 proteinurea 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 NO production.

(609) 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

(610) 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 (RAS). Initial studies suggested that vasoactive compounds like captopril could inhibit radiation induced impairment of renal function in the pig (Robbins and Hopewell, 1986). Extensive studies by the group of Moulder subsequently demonstrated that both ACE inhibitors and AII receptor antagonists effectively inhibited development and progression of renal damage in rats after total body irradiation with bone marrow transplant (TBI/BMT) or after bilateral renal irradiation (reviewed in Moulder et al., 1998; 2007; Robbins and Diz, 2006).

(611) The first studies by the Moulder group 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 proteinurea were reduced and animal survival enhanced in groups treated with either captopril or the non-thiol ACE inhibitor enalapril (Moulder et al., 1993). They subsequently demonstrated that both 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 (Cohen et al., 1994; Moulder et al., 1996; 1998; 1993). 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 brief treatment, from 3.5-9.5 weeks after TBI/BMT. The protective effects of the inhibitors are therefore exerted during the initial development of proteinurea and before the onset of azotemia or increased blood pressure. Both ACE inhibitors and AII receptor antagonists effectively inhibit radiation nephropathy even 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).

(612) These very promising pre-clinical 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

(613) A single injection of Palifermin (recombinant human keratinocyte growth factor, KGF) given 2 days before single dose pelvic irradiation significantly protected against both acute and late bladder dysfunction (Jaal and Dorr, 2007). The ED_{50} for reversible acute damage increased from 20 to 27 Gy and the EC_{50} for late damage increased from 16 to 22 Gy (DMF1.35 and 1.38, respectively). Drug given after irradiation had no protective effect. Palifermin modifies both proliferation and differentiation in epithelial and endothelial cells and transient 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

(614) Comparatively little work has been performed in the area radiation response modifiers in the musculoskeletal system relative to many other organ systems.

Free radical scavengers

(615) 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 has not been evaluated. However, there are concerns related to tumour protection with the use of such compounds.

(616) 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., 2006; 2004). Pentoxifylline alone has been shown to protect against radiation-induced growth plate injury (Pateder et al., 2002).

(617) 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.

(618) 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 anticancer and anti-angiogenic properties, (Kumar et al., 2008). Not unexpectedly, diphosphonate appears to reduce the adverse effect of radiation on bone formation (Ubios et al., 1986),

Growth factors

(619) The growth factor, bone morphogenic protein 2 (BMP-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 BMP-2 and basic fibroblast growth factor (bFGF), when applied alone, enhanced post-radiation bone formation. In contrast, when the two growth factors were given together, they adversely impacted osteogenesis.

Hyperbaric oxygen

(620) Hyperbaric oxygen (HBO) therapy has been shown to have a positive effect in a number of delayed radiation injuries situations, including musculoskeletal radiation injury (Feldmeier and Hampson, 2002). HBO remains somewhat controversial, however, because of the difficulties with endpoint assessment and the problems associated with conducting randomised clinical trials.

Stem cells

(621) 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 myofiber, 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 properties as stem cells. After various types of experimental injury, including radiation injury, satellite cells are capable of proliferating and regenerating new myofibers (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

(622) 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 three to six months (SIGN, 2004). In children who have previously had cranial irradiation, significant growth deviation over a 12 month period (defined as growth velocity below the 25th centile or a drop in height of >1 standard deviation), in the absence of other aetiologies, is highly suggestive of clinically significant GH deficiency.

(623) Children with impaired growth velocity should be tested for growth hormone levels. Growth hormone deficiency is defined by an attenuated GH response to pharmacological stimuli. While 24 hour 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, insulin-like growth factor (IGF-1) and IGF binding protein 3 (IGFBP-3), are consistent, but not specific for GH insufficiency, and may provide additional biochemical information (Shalet et al., 1998).

(624) Growth hormone replacement in children with radiation-induced GH deficiency increases growth velocity and growth hormone 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 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 1988 a,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.

(625) 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 two years after diagnosis. Data from single and large multi-centre surveillance studies showed no increase in the risk of tumour recurrence or incidence of *de novo* malignancies in children treated with GH replacement, initiated two or more years after completion of primary treatment (Swederlow et al., 2000; Price et al., 1998; Shalet et al., 1997). Growth hormone therapy is recommended for children with proven growth hormone deficiency but with a good prognosis at two years after treatment. When the cause of growth impairment is unclear, a trial of GH may be appropriate (SIGN, 2004).

(626) 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 (Mericq et al., 2000; Adan et al., 2000). In children

receiving cranial irradiation only, gain in statural height is a consequence of better spinal growth, however, for those who have received craniospinal irradiation skeletal disproportion may be exacerbated as height gain will be due to leg growth.

(627) Growth hormone 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

(628) Clinical assessment is of limited value in 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 (SIGN, 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.

(629) 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

(630) 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 gonadotrophin secretion

(631) Gonadotrophin deficiency increases with time following cranial irradiation in excess 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 gonadotrophin deficiency; reported in 33% and 66% of five-year survivors following 20 Gy 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 gonadotrophin 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).

(632) All children should undergo regular assessment of pubertal status and Tanner staging as appropriately indicated by age and clinical examination (SIGN, 2004). In post pubertal males, testicular volume <12mls strongly correlates with impaired spermatogenesis. Hormone assessments of serum FSH/LH, testosterone and oestradiol in males and females respectively should also be routinely performed. Inhibin B strongly correlates with sertoli cell function and spermatogenesis in males, and AMH in females reflecting primordial follicle reserve.

(633) Precocious puberty is defined as the development of secondary sexual characteristics at an age that is more than 2 SDs earlier than the population mean; generally accepted as <8 years for girls and <9 years for boys. Low-dose cranial irradiation with doses of $\leq$ 24Gy (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 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 also to maximise the benefit of GH replacement therapy.

3.3.11. Nervous system

Antiinflammatory and anticoagulant agents

(634) 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).

(635) 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 brains (Tada et al., 1997). There is also some anecdotal evidence that the steroidal anti-inflammatory drug meclofenamate 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).

(636) 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., 19883). 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).

(637) 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 PPARα agonists (Ramanan et al., 2008). *In vivo* studies in rats have shown that a PPARγ agonist given before and for 4 or 54 weeks after whole brain irradiation prevented the cognitive impairment induced by 40-45 Gy (given in 8 or 9 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

(638) The brain has a functioning RAS that is involved in modulation of the blood brain barrier, as well as memory and cognition (see Robbins and Diz 2006). AT 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 AT receptor antagonist also prevented or reduced cognitive impairment of rats after fractionated whole brain irradiation (40 Gy in 8 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 only 5 weeks after irradiation significantly reduced but did not eliminate the cognitive impairment (Robbins et al., 2009).

Thiols and radical scavengers

(639) 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

(640) Experimental studies have shown that growth factors including insulin-like growth factor-1 (IFG-1), platelet derived growth factor (PDGF), or basic fibroblast growth factor (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 lead to an increase in the radiation tolerance by about 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).

(641) Hypoxia and increased VEGF expression are associated with breakdown of the blood brain barrier preceeding white matter necrosis and paralysis after spinal cord irradiation (Li et al., 2001). This observation has lead 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

(642) The PUFA (Poly Unsaturated Fatty Acid) Gamma linolenic acid (GLA) was shown to be effective in reducing injury in irradiated pig spinal cord, with approximately a 10% increase in tolerance dose (Hopewell et al., 1994b). Gamma linolenic acid was subsequently tested in conjunction with radiosurgery for patients with large arterioveneous malformations (Sims and Plowman, 2001). The GLA treated group had significantly less permanent complications, but they also had less effective obliteration of the lesions, therefore there was no overall therapeutic gain.

(643) Vasoactive drugs like dipyridamole (increases blood flow and reduces thrombosis) and desferrioxane combined with 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 about 10% in rats (Hornsey et al., 1990).

Stem cells

(644) Rezvani and colleagues showed that transplantation of neural progenitors could be used to ameliorate radiation-induced myelopathy in rats (Rezvani et al., 2001). Immortalized 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 so the biological mechanisms for the effect are not yet clear.

3.4. References Chapter 3

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4. THRESHOLD DOSES IN RELATION TO RADIOSENSITIVITY OF ORGANS AND TISSUES

4.1. Introduction

(645) The recommended dose limits for tissue reactions (deterministic effects) are based on 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, 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.

(646) Recently, a survey has been completed of organ tolerances to fractionated radiotherapy treatments (Marks et al., 2010). This information is summarised in Table 4.1, and it 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.

(647) In the recent ICRP recommendations (ICRP, 2008), 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.

(648) This report has not considered tissue reactions after high-LET irradiations. These were described in detail in ICRP 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 (NCRP, 1990), and for particular applications such as radiotherapy e.g. IAEA (IAEA, 2008).

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 summarized 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 D_{max} =72	<3 5
Brain stem	Neuropathy or necrosis	D_{max} <54	<5
Optic nerve/chiasm	Neuropathy	D_{max} <55 D_{max} 55-60	<3 3-7
Spinal cord [a]	Myelopathy	D_{max} =50 D_{max} =60	0.2 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 [b] D_{mean} <44 V_{50} <27 %	<20
Lung	Pneumonitis	V_{20} <30 % D_{mean} = 7 D_{mean} = 13	<20 5 10
Oesophagus	Oesophagitis grade 3 Oesophagitis grade 2	D_{mean} <34 V_{35} <50 %	5-20 <30
Heart	Pericarditis Long-term mortality	D_{mean} <26 V_{30} <46 % V_{25} <10 %	<15 <1
Liver [c]	Radiation-induced liver disease	D_{mean} <30-32	<5
Kidney	Renal dysfunction	D_{mean} <15-18 V_{12} <55 % V_{20} <32 %	<5
Stomach	Ulceration	D_{100} <45	<7
Small bowel	Grade 3 acute toxicity	V_{45} <195cc	<10
Rectum	Grade 2 late toxicity Grade 3 late toxicity	V_{50} <50 %	<15 <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
[a] Partial organ irradiation, including full cord cross-section
[b] With chemotherapy
[c] Excluding patients with pre-existing liver disease

4.2.Haematopoietic system

(649) Acute threshold doses of about 0.5 Gy, and chronic dose rates of 0.4 Gy per year, remain as recommended values for depression of haematopoiesis (Section 2.1). Also for mortality, the threshold values of about 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.

(650) 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 to 3 months (UNSCEAR, 1988).

(651) 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 radiation accident victims. 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

(652) 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).

(653) 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. 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 to 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).

(654) 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

(655) The threshold doses for males for acute, fractionated/protracted, and chronic exposures (Table 4.3), and the bases for these doses, remain virtually the same as recommended in the last review of deterministic effects by ICRP (ICRP 41, 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 versus others for medical application (Section 3.3.3).

(656) The threshold doses for females for acute, fractionated/protracted, and chronic exposures (Table 4.3) remain the same as previously recommended by ICRP (ICRP 41, 1984). It is noted that sensitivity increases as age increases, 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

(657) The radiation response of the skin was documented extensively in ICRP 59 (ICRP, 1991) and summarised in ICRP 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.

(658) 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 polyunsaturated fatty acids have shown promise for reducing early reactions. For reducing late reactions, SOD, FGF, captopril, polyunsaturated

fatty acids, α-tochopherol and inhibition of TGFβ signalling, have shown some promise in both humans and animal systems. The dose modification factor (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 system

(659) Circulatory disease has not been previously 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 more than 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 excess relative risk for cardiovascular disease is greater than that for stroke or cerebrovascular disease (Section 2.5).

(660) A review in 2007 (Schultz-Hector and Trott, 2007) concluded that the atomic bomb and the 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 extrapolation procedure is only approximate, because the value of the fractionation sensitivity parameter relies on rodent data, although human data for a pericarditis endpoint do indicate an α/β ratio of 2.5 Gy which is consistent with the values for rodents (Section 2.5.3). Also, it is not known if the average dose to the heart is the most appropriate metric. Nonetheless, this first approximation showed that the relative risk data for heart disease after heart exposures from atomic bombs, peptic ulcer and breast cancer radiotherapy were similar. This composite analysis indicated a small acute-dose threshold of around 1 Gy. Above this dose, the excess risk per Gy increased with increasing dose. This would be expected if a linear-quadratic relationship was applicable (see Appendix B). 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 to 0.5 Gy, the dose response was not statistically significant, indicating that the low-dose data are weak. For stroke, the estimated threshold doses was 0.5 Gy, with an upper 95% confidence limit of 2 Gy.

(661) 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., 2009). This more rigorous statistical evaluation of a larger number of data sets than evaluated previously by Schultz-Hector and Trott (2007) indicated that heterogeneity was reduced, but remained significant,

when adjustments were made in the analysis 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. less than 5 Gy) was viewed by Little et al. (2009) as being suggestive rather than persuasive and no dose threshold analysis was made.

(662) In the Introduction to this report, the term *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.

(663) As was stated in section 2.5.2, circulatory diseases account for 30-50% of all deaths in most developed countries. For example, about 33% of all deaths in the UK are due to circulatory disease (www.heartstats.org). Whilst the estimates of the excess relative risk (ERR) per 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 A-bomb study. In particular, 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, then this would imply that a dose of 0.5 Gy might increase mortality from circulatory disease by around 0.08 x 0.5 x (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. Consequently, subject to the assumptions outlined here, a dose of around 0.5 Gy might lead to roughly 2% of exposed individuals developing circulatory disease.

(664) 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 (around 1 in 6 of deaths in the UK – AGIR, 2010) is greater than that for cerebrovascular disease (around 1 in 9 of deaths in the UK – AGIR, 2010), then as the ERR/Gy may be greater for cerebrovascular disease than for cardiovscular 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 roughly 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.

(665) 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 appropriate, and future research may elucidate this further.

(666) It is unclear whether or not the ERR/Gy is the same for acute, fractionated and chronic exposures. On the basis of the LQ model, 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 (alpha kill) injury, with no split-dose repair, slow repair or cell repopulation effect involved at these very low dose levels (see Appendix B). In addition, some published radiotherapy data indicate very much higher threshold doses. This is due in part to the shorter follow-up times of about 15 years. 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 of the atomic bomb survivors (40-50 years followup), 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 (see Appendix B).

(667) For the purposes of this assessment, the ERR/Gy and hence the "threshold dose" will be taken to be the same for all three types of exposure, i.e. around 0.5 Gy. Future studies may elucidate this further. For chronic occupational exposure over a working life of not more than 40 years, this total dose would equate to an annual dose of 12 mGy.

(668) For perspective, the estimated risk of fatal cancer associated with 40 years' occupational exposure to a whole-body dose of 12 mGy (low LET) per year, assuming a nominal risk coefficient for workers of 4% per Sv, would be 2%. For a population of all ages with a cumulative whole-body dose of 0.5 Gy (low LET) arising from chronic exposure, then 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.

(669) The mechanisms of radiation induced heart damage include inflammatory processes, in particular after low doses, and 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, used generally to treat heart conditions, glutamine supplementation, and laboratory research is further investigating the benefits of stem cell transplantation or stem cell products.

4.7. Eye

(670) A recent review of epidemiological studies of radiation induced cataracts (Ainsbury et al., 2009) included eight studies published since 1999 that estimated odds ratios or relative risks for cataract development at 1 Gy or 1 Sv, or comparisons of exposed and unexposed groups (Figure 4.1). 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).

(671) Formal estimates of acute threshold doses (Table 4.2) 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% confidence intervals 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 0.34-0.50 Gy, with 95% confidence intervals 0.17-0.69 Gy. There was no dependence of threshold dose on stage or site of the cataract. Regarding chronic irradiation, there have been studies of diagnostic radiation technologists, commercial pilots and astronauts and residents of radioactive buildings in Taiwan. These studies generally are not 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 statistically significant extent.

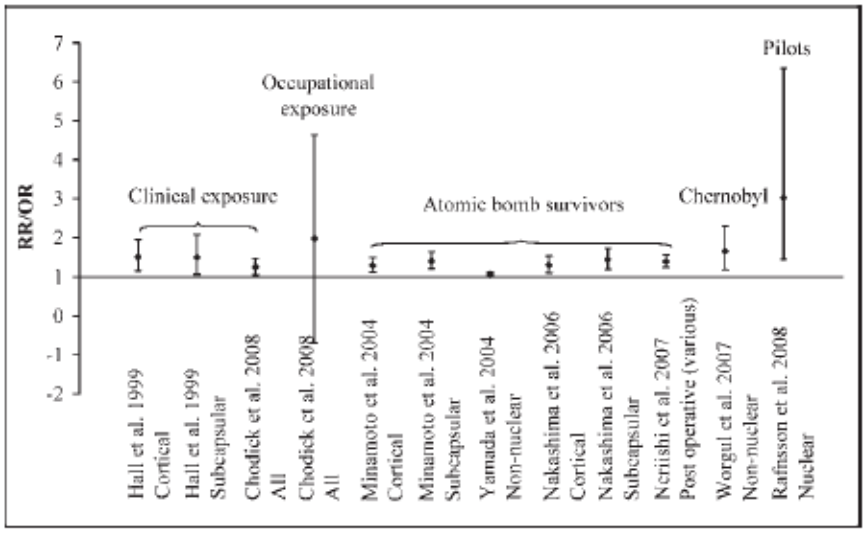

Fig. 4.1. Odds ratio or relative risk for cataract development, either at 1 Gy or 1 Sv or from comparisons of exposed and unexposed groups, by study, cataract type and exposure group (Ainsbury et al., 2009).

Table 4.2. Recent epidemiological studies of cataract formation where formal estimates of threshold doses were made.

Study	Cataract type	Threshold dose	Confidence intervals	Reference
A bomb survivors (acute exposure)	Cortical cataracts	0.6 Sv	90%: <0-1.2 Sv	Nakashima et al., 2006
	Posterior subcapsular opacity	0.7 Sv	90%: <0-2.8 Sv	
A bomb survivors (acute exposure)	Postoperative cataracts	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	

(672) 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. Earlier it was 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. 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.

(673) 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 cataract, an increased frequency of micronuclei (a marker of impaired cell division) has been reported, and in animals it has been shown that radiation cataract will not form if epithelial cell division is totally inhibited or the dividing epithelial cells are shielded from radiation exposure. It can be speculated that radiation cataract formation could be explained by initial damage to single progenitor epithelial cells in the lens which, upon cell division and differentiation, result in groups of defective lens fibre cells. Future research may elucidate the true mechanism of cataract formation.

(674) In ICRP Publication 103 (ICRP, 2008), 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 studies on the atomic bomb survivors and radiotherapy patients available at an earlier time (ICRP, 1984). These early studies of radiation cataract generally had short follow-up periods, failed to take into account 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 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 cataract. A summary of results of many of the studies of radiation-induced lens changes (Section 2.6.1 and Appendix A) is shown in Table 4.3.

(675) In view of the above problems with the early studies of radiation cataract 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 4.2) for induction of opacities or cataracts show the following values with wide confidence intervals:

- 500-700 mSv in the 2006 A-bomb study, for early PSC and cortical opacities (Nakashima et al., 2006)
- 100 mSv in the 2007 A-bomb study, for cataract surgery prevalence (Neriishi et al., 2007)
- 450-500 mSv for the EAR & ERR models respectively, in the 2010 A-bomb study for cataract surgery incidence, which is stronger than the prevalence study (Nakashima et al., 2010; Blakely et al., 2010).

Furthermore, infants treated with Ra-226 plaques for hemangioma and who received a mean dose 400 mGy, showed a dose-response with a RR at 1 Gy of 1.5 for cortical opacities and 1.5 for PSC opacities (Hall et al., 1999).

Table 4.3 Summary of results of many of the studies of radiation-induced lens changes.

Author	No.	Age at exposure (years)	FU time (years)	Dose range or average (Gy)*	Fractions	Results	Comments
Treatments							
Cogan et al., 1953	40	15-70	7 (1-14)	0.23-24	1 to n	5 cats None < 5 Gy	Small case series, short FU
Merriam et al., 1957	100	0.9- 84	5-9	0.25-69	1 to n	All cats > 2 Gy or fractions > 5 Gy	Clinical series, n=33 at < 200 r, short FU
Qvist et al., 1959	56	Infants	>20-40	>1	1-15	4 cats at >6.9 Gy	Small study
Albert et al., 1968	234	8 (1-14)	10	0.5	5 (over a few	13 opacities	Small study

					minutes)		
Wilde and Sjostrand, 1997	20	0.2-1	30-46	1-11 Ra-226	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) Ra-226	2 (1-14)	Cats vs. dose	Cortical not nuclear vs. dose
A-bomb survivors							
Cogan et al., 1950	1,000	All	4	NA	1	Some opacities	Screening study
Choshi, 1983	2,385	All	33-35	>1	1	Increased opacities	No dose-response estimated
Otake, 1996	~2,000	All	18-19	NA	1	Various opacities/ cataracts	Screening study
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	3,761	0->20	55-57	0- >3	1	Threshold 0.1 (0-0.8) Gy	12.7% cataract surgery
Accidents, residents							
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	Cats at 3.2 Gy	Small study
Worgul et al., 2007	8,607	Adults	12-14	0-1	Protracted	Opacities	Chernobyl clean-up workers
Hsieh et al., 2010	73	<20	4.7	~0.200 Sv	~7 y	Some opacities	Residential exposure
Workers							
Junk et al., 2004	59	NA	5-36	NA	5-36 y	Cats at long times	Chronic exposure
Shang et al., 2007	584	20-57	0.3 -35	NA	0.4-35 y	Opacities at long times	Chronic exposure
Chodick et al., 2008	35,705	Workers	~19	0.005-0.06	6-13 y	Cats at higher dose	RT's self reporting
Kleiman et al., 2009	78	IC workers	1-40	NA	Chronic	Some opacities	Doses unknown

* or Sv where stated; No = number of subjects; n = number (many) fractions; FU = follow-up time; cats = cataracts; RT = Radiologic Technologists; IC = Interventional Cardiologists. See Appendix A for further details. Information courtesy of Dr. R.E. Shore, RERF, Hiroshima, Japan.

(676) For fractionated, protracted irradiation, an accumulated dose threshold of 350 mSv 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.

(677) 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 USA radiologic technologists receiving highly fractionated cumulative doses of 5 mGy to 60 mGy, it was reported that the incidence of cataracts was marginally higher in the 60 mGy dose group than in the 5 mGy group, and that 3 or more diagnostic x-rays to the face/neck at baseline showed a significant elevation in subsequently reported cataracts (Chodick et al., 2008). In American 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 (Chylack et al., 2009; Cucinotta et al., 2001). An excess of early and progressing opacities was found in young (<20 year old) residents of Co-60 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 ~200 mSv (median dose ~ 54 mSv) over ~7 years (Chen et al., 2001; Hsieh et al 2010).

(678) 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 500 mSv. 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 to post-adolescents, both require further characterisation.

(679) For fractionated and protracted exposures, the current epidemiological evidence indicates that the threshold is not larger than 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.

(680) In addition, it is suggested that there is a genetic component to the radiosensitivity of cataractogenesis, which may produce more cataracts in a few percentage 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% confidence interval 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

(681) 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).

(682) 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

(683) 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 about 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 linear-quadratic model are problematic, to a first approximation these values are compatible with the value of the fractionation sensitivity parameter α/β=2.5 Gy deduced from studies using animal systems.

(684) For late reactions in the bladder, the threshold total fractionated (2 Gy fractions) dose is$\leq$ 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 around 15 Gy single dose. For the ureters, the threshold total fractionated dose is also suggested to be $\leq$ 50 Gy.

(685) 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. Antiinflammatory 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

(686) Radiation exposure can give rise to three different types of non-cancerous bone pathologies, namely 1) osteoradionecrosis, 2) spontaneous fractures or fractures with less than normal trauma, or 3) 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 about 55 Gy (2 Gy fractions) has been estimated (Section 2.9).

(687) Hyperbaric oxygen (HBO) therapy has been shown to have a positive effect in a number of delayed radiation injuries 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 researched in preclinical systems.

4.11. Endocrine system

(688) 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 of generally 2 Gy per fraction. The hypothalamus is more radiosensitive than the pituitary. In children, radiation effects include growth hormone deficiency, precocious puberty (after lower doses) or delayed puberty (after higher doses), hypopituitarism, and hyperparathyroidism. In adults, radiation effects include hyperprolactinemia, hypogonadism, obesity, hypothyroidism, hyperthyroidism, and ACTH deficiency.

(689) There are various strategies for mitigating the effects of radiation on the endocrine system. These include growth hormone (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 gonadotrophin secretion after pituitary damage. However there is insufficient evidence of the efficacy of these procedures in order to calculate a radiation dose modifying factor.

4.12. Nervous system

(690) The threshold dose for symptomatic spinal cord injury (myelitis) is about 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 lenth) 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 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 imparment in adult life detected after exposure to doses >100 mGy before 18 months (Section 2.11).

(691) There are no recognised mitigating agents for use in humans to treat spinal cord injury after irradiation. Pre-clinical studies with anti-inflammatory agents, ACE inhibitors and AII receptor antagonists, some growth factors, and polyunsaturated fatty acids, 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

(692) This ICRP report has produced some changes to indicated threshold doses for tissue reactions, compared to those stated in ICRP 103 (ICRP, 2008). First, the threshold dose for radiation-induced eye cataracts is now considered to be around 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 around 0.5 Gy has been proposed for acute, and fractionated/protracted exposures, on the basis that this might lead to circulatory disease within a few percent of exposed individuals, although the estimation of risk at this level of dose is particularly uncertain.

(693) 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 makes 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 more than 10 years followup. Future studies may elucidate this further. For the public the annual threshold dose values would be scaled down in proportion to relative lifespan minus latency period (20 years latency for lens, 10 years for circulatory disease) versus working life. It is emphasised that great uncertainty is attached to these values.

(694) 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.

(695) As a general conclusion, the ICRP judges on the basis of existing evidence, that acute doses up to around 100 mGy produce no functional impairment of tissues. This includes the lens of the eye regarding the risk of cataract, with the caveat that for this tissue the use of a threshold model remains uncertain. 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, in particular regarding radiation incidents and accidents, and medical exposures.

13037
13038
13039 Table 4.4. Estimates of the threshold doses[a] for approximately 1% incidence in
13040 **morbidity** in tissues and organs in adults exposed to acute, fractionated or
13041 protracted, and chronic irradiation.
13042

Effect	Organ/tissue	Time to develop effect	Acute exposure (Gy)	[b]Highly fractionated (2 Gy per fraction) or equivalent protracted exposures (Gy)	Annual (chronic) dose rate for many years (Gy y^{-1})
Temporary sterility	Testes	3-9 weeks	~0.1	NA	0.4
Permanent sterility	Testes	3 weeks	~6	<6	2.0
Permanent sterility	Ovaries	< 1week	~3	6.0	>0.2
Depression of haemopoiesis	Bone marrow	3-7 days	~0.5	~10-14Gy	>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 to 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 @ 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[c]
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

[a]Most values rounded to nearest Gy; ranges indicate area dependence for skin and differing medical support for bone marrow; NA= Not Available.

[b]Derived in most cases from fractionated radiotherapeutic exposures, generally using 2 Gy per fraction. 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 per minute 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; van der Kogel, (2009).

[c] The values quoted for the lens assume the same incidence of injury irrespective of the acute or chronic nature of the exposure, with more than 20 years followup. It is emphasised that great uncertainty is attached to these values.

*Table 4.4. Estimates of the threshold doses for **mortality**[a] in adults exposed to acute, fractionated or protracted, and chronic irradiation.*

Effect	Organ/tissue	Time to develop effect	Absorbed dose[b] resulting in about 1% incidence		
Mortality:			Acute exposure (Gy)	[c]Highly fractionated (2 Gy per fraction) or equivalent protracted exposures (Gy)	Annual (chronic) dose rate for many years (Gy y^{-1})
Bone marrow syndrome:					
- without medical care	Bone marrow	30-60 days	~1	10	NA
- with good medical care	Bone marrow	30-60 days	2-3	>10	NA
Gastro-intestinal syndrome:					
- 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

[a]Some of these diseases are not always fatal, as noted in the Table by the use of good medical care and implied for the future by the increasing success in some pre-clinical animal systems of the use of various biological response modifiers (see Section 3). In the cases of cardiovascular disease and cerebrovascular disease, from the evidence currently available the values given here are assumed to apply also to morbidity from these diseases.

[b]Most values rounded to nearest Gy; ranges indicate area dependence for skin and differing medical support for bone marrow; NA= Not Available.

[c]Derived from fractionated radiotherapeutic exposures, generally using 2 Gy per fraction. 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 per minute 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; van der Kogel, 2009.
[d] The values quoted for the circulatory system assume the same incidence of injury irrespective of the acute or chronic nature of the exposure, with more than 10 years followup. It is emphasized that great uncertainty is attached to these values.

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APPENDIX A. SUMMARY OF STUDIES OF EXPOSURE AND OPACITIES OR CATARACTS

(A 1) This review was compilled by Dr. Roy E. Shore, RERF, Japan and primarily relates to low-LET radiation.
(Note: Articles are in chronological order, except that the chronological series of Japanese atomic bomb studies are listed together at the end.)

Author and date	**Cogan & Dreisler, 1953**
Reference	Cogan DG, Dreisler KK. Minimal amount of x-ray exposure causing lens opacities in the human eye. AMA Arch Ophthalmol. 1953;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 y to 70 y
Gender distribution	70% females
Participation rate	N/A
Dose	23-2400 R (estimates based on phantom reconstructions)
Radiation type	100-200 kV x-ray (except 1 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 y (53% under 30 y)
Follow-up time	1.3-14 y (Means = 7.3 y overall & 8.0 y for those without cataract)
Confounders evaluated?	None
Description of results	5 radiation cataracts noted. None among the 33 persons with <500 R
Threshold dose (Conf intervals)	--
Prevalence at 1 Gy (95% CI)	--
Comments	Small irradiated case series, with a short follow-up time

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Author and date	**Merriam & Focht, 1957**
Reference	Merriam GR, Focht EF. A clinical study of radiation cataracts and the relationship to dose. *Am J Roentgenol, Radium Ther Nucl Med*. 77:759-84, 1957 (Also: Merriam GR, Szechter A, Focht E. The effects of ionizing radiations on the eye. *Front Radiat Ther Oncol*. 1972;6:346-385)
Type of study	Case series from clinical records
Number of individuals	Searched clinical records for 100 persons with radiation opacities/cataracts + found 73 with head irradiation (x-ray or radium) & no lens opacities
Ages at exposure	1 mo. to 84 y.
Gender distribution	49% females
Participation rate	N/A
Dose	Based on retrospective dose reconstruction with a phantom; Range 25 r to 6900 r; In cataract group: 0% <200r, 4% 200-350r, 26% 400-1000r, 19% 1000-2000r, 11% 2000-4000r, 11% >4000r, 29% dose unknown (but nearly all >1500r); In non-cataract group: 33 (45%) <200r, 11 (15%) 200-399r, 27 (37%) 400-999r, 2 (3%) >1000r
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 RT over 3wk to 3mo, 49 >3mo
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"; categorized them as "stationary" or "progressive" cataracts
Ages at observation	2y to >85y
Follow-up time	Diagnoses of cataract, mean = 4.8 y after 1st RT; Those without cataract & with estimated lens dose <200 r, last eye exam, mean = 9.3 y after RT
Confounders evaluated?	Examined age-at-exposure effect; informally considered complicating factors (hemorrhage, glaucoma, uveitis)
Description of results	All cataract cases had estimated doses >=200 r. For cataracts after divided exposures of >3 mo, the minimum dose was >500 r. Reported an inverse relation between lens dose & time to cataract, and greater sensitivity among those young at exposure (findings based on crude tabulations & no statistical testing).
Threshold dose (Conf intervals)	Indicated 200 r for any opacity; about 500 r 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 under 200 r was grossly inadequate (only 33) and the follow-up times after irradiation were short (mean= 9.3 y). Though this became the major basis for radiation standards for several decades, by modern day epidemiologic standards the study would be regarded as substantially inadequate.

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Author and date	**Qvist and Zachau-Christiansen, 1959**
Reference	Qvist CF, Zachau-Christiansen B. Radiation cataract following fractioned radium therapy in childhood. Acta Radiol. 51:207-216, 1959.
Type of study	Sample of a cohort who had received radium therapy for hemangiomas
Number of individuals	855 patients with treatment to the head; selected the 112 who were estimated to have received a lens dose >100 r. Of those, examined 56
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 to 15 treatments (over up to 10+ months)
Technique for assessment	Ophthalmological examination (methods unspecified)
Endpoint	Cataract
Ages at observation	Not specified (>20 to >40)
Follow-up time	Not specified (>20 to >40y)
Confounders evaluated?	None noted
Description of results	"4 cases of unmistakable radiation cataract", all with doses >=690 r. However, in addition, one opacity was found with an estimated dose of 10-35 r, which they did not consider to be a "radiation cataract", 1 "senile cataract" at age 40 with a dose of 640 r, and 1 "congenital cataract" with a dose of 25 r.
Threshold dose (Conf intervals)	They considered 690 r as their threshold.
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 r.

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Author and date	**Albert et al., 1968**
Reference	Albert R, Omran A, Brauer E, Cohen N, Schmidt H, Dove D, et al. Follow-up study of patients treated by x-ray epilation for tinea capitis. II. Results of clinical and laboratory examinations. Arch Environ Health, 1968;17:919-934.
Type of study	Screening of subsample of irradiated cohort
Number of individuals	234 radiation-exposed, 232 unexposed
Ages at exposure	1-14 y, mean= 7.7 y
Gender distribution	10% females
Participation rate	~50%
Dose	Eye dose ~500 mGy
Radiation type	X ray
Dose rate	5 unequal fractions a few minutes apart
Technique for assessment	Slit-lamp exam. Examiner blinded as to radiation status.
Endpoint	Abnormal luminescesce & early PSC opacities
Ages at observation	Median 17 y (68% ages 10-19, 32% 20+y)
Follow-up time	~10y
Confounders evaluated?	Sex, race (37% blacks, 63% whites), age
Description of results	Exposed vs. nonexposed: No difference for abnormal luminescence or non-PSC opacities. PSC opacities: 13 irradiated & 2 control cases (Age-adjusted OR= 5.9, 95%CI: 1.4-24); PSC opacities were "very mild".
Threshold dose (Conf intervals)	--
Prevalence at 1 Gy (95% CI)	--
Comments	Small study of opacities at young ages after ~0.5 Gy eye dose from x-ray.

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Author and date	**Day et al., 1995**
Reference	Day R, Gorin MB, Eller AW. Prevalence of lens changes in Ukrainian children residing around Chernobyl. *Health Phys*, 68(5):632-642, 1995
Type of study	Cross-sectional prevalence study
Number of evaluable	991 from 2 towns/areas with high depositions; 791 from a

individuals	town with virtually no deposition
Ages at exposure	Ages 0-12
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 to 148 x10^{10} Bq km^{-2} (or m^{-2} ??); estimates of cumulative dose 1986-89 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% ages 5-11y; 51% 12-17y
Follow-up time	5.7 y
Confounders evaluated?	Diabetes, radiotherapy, daily medications
Description of results	No difference in cortical opacities >=2 [exposed 15 (1.5%), unexposed 10 (1.3%)]; PSC >=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 (Conf intervals)	--
Prevalence at 1 Gy (95% CI)	--
Comments	Ophthalmologists knew of the subjects' exposure status. However, they had standardization, retraining & reliability evaluation, examination of positive lenses by 2 examiners, plus slit-lamp photographs of positive lenses.

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Author and date	**Wilde & Sjostrand, 1997**
Reference	Wilde G, Sjostrand J. A clinical study of radiation cataract formation in adult life following □ irradiation of the lens in early childhood. Br J Ophthalmol 1997;81:261-266.
Type of study	Opacity prevalence in a small cohort treated with ^{226}Ra for hemangioma of the eyelid
Number of individuals	20
Ages at exposure	2-13 mo.
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 to 3 h
Technique for assessment	Slit-lamp biomicroscopy & retroillumination photography
Endpoint (subgroups?)	"radiation cataract"

Ages at observation	31-46 y
Follow-up time	30-46 y
Confounders evaluated?	None noted
Description of results	No formal statistics. All treated eyes had opacities; found that opacity grade increased with lens dose. 13 of 20 contralateral lenses had very minor opacities.
Threshold dose (Conf intervals)	--
Prevalence at 1 Gy (95% CI)	--
Comments	Carefully conducted, but small study contributes little quantitative information

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Author and date	**Hall et al., 1999**
Reference	Hall P, Granath F, Lundell M, Olsson K, Holm L-E. Lenticular opacities in individuals exposed to ionizing radiation in infancy. *Radiat Res*, 152:190-195, 1999
Type of study	Cohort study, screening prevalence
Number of individuals	484 exposed; 89 nonexposed
Ages at exposure	Mean 5 months; range 0-16 mo.
Gender distribution	Exposed 72% females; nonexposed 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, max. 3.0 Gy/h
Technique for assessment	LOCS system; score >=1 considered positive
Endpoint (subgroups?)	Cortical & PSC opacities
Ages at observation	46 y (range 36-54)
Follow-up time	46 y
Confounders evaluated?	diabetes; steroid Tx; family history of cataract; other eye disorder; other radiotherapy
Description of results	Cortical+PSC cataract prevalence by dose (mGy): 0= 9/178 (5%), 0- = 89/747 (12%), 500- = 20/115 (18%), 1000+ = 20/89 (22%)
Threshold dose (Conf intervals)	--
Prevalence at 1 Gy (95% CI)	Cortical: 1.50 (1.15-1.95); PSC: 1.49 (1.07-2.08)
Comments	Nuclear cataracts were not related to radiation dose. Dose-response analysis was limited to exposed group, because nonexposed group was insufficiently comparable.

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Author and date	**Nadejina et al., 2002**

Reference	Nadejina NJ, Galstian IA, Savitsky AA, Kashirina OG, Rtisheva JN, Uvatcheva IV, Ivanova EY. Non-stochastic follow-up effects of Chernobyl accident recovery workers. In: Chronic Irradiation: Tolerance and Failure in Complex Biological Systems. Brit. J. Radiol. 50-54, 2002.
Type of study	Cohorts of 13 Acute Radiation Syndrome (ARS) persons & 30 recovery operations workers
Number of individuals	11 ARS & 30 recovery workers
Ages at exposure	Mean ~35y for ARS, ~37y for recovery workers
Gender distribution	<10% females
Participation rate	Complete
Dose	ARS minimum dose 2.6 Gy, average estimated as ~3.2 Gy. Recovery workers, estimated mean 0.2 Gy
Radiation type	Gamma and beta
Dose rate	ARS, high dose rate; recovery workers protracted
Technique for assessment	Repeated ophthalmologic exams over 14 y (instrumentation not specified)
Endpoint	Cataracts
Ages at observation	Up to 14 years older than exposures
Follow-up time	About 14 y
Confounders evaluated?	None
Description of results	5 of 11 ARS cases had radiation cataracts. Reported no radiation cataracts, but 3 senile cataracts in the recovery workers.
Threshold dose (Conf intervals)	--
Prevalence at 1 Gy (95% CI)	--
Comments	They mention a Russian language publication that reported 13 cataract cases in ARS subjects.

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Author and date	**Junk et al., 2004**
Reference	Junk AK, Haskal Z, Worgul BV. Cataract in interventional radiology – an occupational hazard? Invest Ophthalmol Vis Sci, 45:E-abstract 388, 2004
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
Dose rate	Occupationally exposed from 5 to 36 y
Technique for assessment	Scheimpflug examination after pupil dilation
Endpoint	Pre-cataract changes & PSC cataracts
Ages at observation	29 to 62 y
Follow-up time	No follow-up, but had been exposed beginning 5 to 36 y previously
Confounders evaluated?	Age, handedness
Description of results	22 showed "small paracentral dot-like opacities" in PSC region, & PSC cataracts found in 9 eyes of 5 persons. Concluded: frequency & severity of PSC opacities increased with age & number of years in the field
Threshold dose (Conf intervals)	--
Prevalence at 1 Gy (95% CI)	--
Comments	Suggestion that chronic radiation exposure may lead to opacity formation. No dose estimates.

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Author and date	**Shang et al., 2007**
Reference	Shang B, Fu E. Investigation on incidence of lens opacity in radiation workers. Chinese J Indust Med. 20(1):48-49, 2007 (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 mo. to 35y (mean= 11.6 y)
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 to 57y

Follow-up time	4 mo. to 35 y
Confounders evaluated?	Not specified in the summary available. No indication that age was adjusted for.
Description of results	Found increase in more advanced (but still early) opacities with longer radiation-working time.
Threshold dose (Conf intervals)	--
Prevalence at 1 Gy (95% CI)	--
Comments	The study does not provide sufficient quantitative information, but suggests some concern regarding radiation workers, at least with past levels of radiation exposure.

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Author and date	**Worgul et al., 2007**
Reference	Worgul BV, Kundiyev YI, Sergiyenko NM, Chumak VV, Vitte PM, Medvedovsky C, Bakhanova EV, Junk AK, Kyrychenko OY, Musijachenko NV, Shylo SA, Vitte OP, Xu S, Xue X, Shore RE. Cataracts among Chernobyl clean-up workers: Implications regarding permissible eye exposures. Radiat Res. 2007; 167:233-243. (See also: Chumak VV, Worgul BV, Kundiyev YI, Sergiyenko NM, Vitte PM, Medvedovsky C, et al. Dosimetry for a study of low-dose radiation cataracts among Chernobyl clean-up workers. Radiat Res. 2007;167:606-14.
Type of study	2 ophthalmological screenings of an occupationally exposed cohort of Chernobyl cleanup workers
Number of individuals	8,607 screened twice
Ages at exposure	8.5% <25 y old (yo), 14% 25-, 23% 30-, 34% 35-, 53% 40+ yo
Gender distribution	4% females
Participation rate	11,797 lived in relevant oblast & had address information; 73% of those were examined
Dose	0 to >1 Gy (2% received >0.7 Gy)
Radiation type	Gamma & beta
Dose rate	Exposures over 1 to several months
Technique for assessment	Ophthalmoscopic and slit-lamp assessment. Ophthalmologists were trained for standardized 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% <40yo, 50% 40-, 14% 50-, 10% >=55yo
Follow-up time	Exams at 12 & 14 y after cleanup work begun (1986-87)

Confounders evaluated?	Smoking, age, sex, diabetes, corticosteroids, occupations with exposure to chemicals, radiation, UVR, 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 (Conf intervals)	Stage 1 posterior cortical opacity, 0.34 Gy (95%CI: 0.18-0.51); Stage 1 PSC opacity, 0.35 Gy (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 (1.09-2.10); Stage 1 PSC opacity, 1.42 (1.01-2.00)
Comments	Variations among examiners were adjusted for, but no photographs of lenses were taken. Nearly all opacities were mild & did not affect vision, but ages were still young. Individual doses were mostly estimated from "official doses" with adjustments based on a limited comparative set of EPR dose estimates, and not actual dosimeter readings, so dose individual dose uncertainties were substantial (cf. Chumak et al, 2007).

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Author and date	**Chodick et al., 2008**
Reference	Chodick G, Bekiroglu N, Hauptmann M, Alexander BH, Freedman DM, Doody MM, Cheung LC, Simon SL, Weinstock RM, Bouville A, Sigurdson AJ. Risk of cataract after exposure to low doses of radiation: a 20-year prospective cohort study among US radiologic technologists. Am J Epidemiol. 2008;168:620-631.
Type of study	Mail questionnaire self-reports of cataracts among radiologic technologist cohort
Number of individuals	35,705 workers with usable data
Ages at exposure	14 to 43 before entry to study
Gender distribution	83% females
Participation rate	54% of those eligible
Dose	Considered number of x-rays to the face/neck, & estimated cumulative occupational radiation exposure
Radiation type	Primarily x-ray exposure
Dose rate	Highly fractionated, over <6 to >13 y
Technique for assessment	Mail surveys of cataracts and numerous potential risk factors
Endpoint	Reported cataract & reported cataract surgery
Ages at observation	~43 to 64 y
Follow-up time	19.2 ± 1.8 y
Confounders evaluated?	>20 variables, including sociodemographic, lifestyle & medical/medication history, & UV exposure index

Description of results	2,382 cataracts reported (591 before age 50 y) & 647 cataract extractions (183 before age 50). Found that those who reported >=3 diagnostic x-rays to the face/neck on the baseline questionnaire subsequently had greater cataract incidence (hazard ratio (HR)= 1.25 (95%CI: 1.06, 1.47, p<0.01). Radiotherapy to the head before age 15: HR= 1.41 (1.00, 1.99) (after age 15 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 (1.09, 2.06). Radiotherapy to head/neck, HR= 1.71 (1.09, 2.68) Occupational radiation exposure: dose-response, ERR/Gy 1.98 (95%CI: -0.69, 4.65, p=0.15). Those in highest vs. lowest dose categories (means of 60 vs. 5 mGy), HR= 1.18 (0.99, 1.40, p=0.06). For cataract surgery, ERR/Gy = 1.50 (-3.43, 6.43)
Threshold dose (Conf intervals)	Found marginally statistically significant difference between workers in highest (Mean= 60 mGy) & lowest (mean= 5 mGy) dose categories
Relative risk at 1 Gy (95% CI)	For total reported cataracts, HR/Gy= 1.98 (-0.69, 4.65). For cataract extractions, HR/Gy= 1.50 (-3.43, 6.43)
Comments	A large study. Based on self-reported cataracts & cataract surgeries. Probably appreciable dose uncertainties, especially for those employed before about 1955 when there was limited film-badge information.

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Author and date	**Kleiman et al., 2009**
Reference	Kleiman NJ, Cabrera M, Duran G, Ramirez R, Duran A, Vano E. Occupational risk of radiation cataract in interventional cardiology. Invest Ophthalmol Vis Sci, Presentation abstract 511/D656, 2009.
Type of study	Cross-sectional screening study
Number of individuals	78 medical interventional cardiology (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 exam after pupil dilation; scored by 3 independent observers
Endpoint	PSC lens changes and opacities
Ages at observation	22 to 69 y for IC physicians (mean 46.7y); 20 to 58 y for other personnel (mean 32.2 y)

Follow-up time	1 to 40 y of experience in IC
Confounders evaluated?	Obtained medical history, but not used in analysis
Description of results	18/42 IC physicians had PSC changes consistent with radiation exposure (10/18 had bilateral changes, 12/18 seldom/never used eye protection, 13/18 didn't use leaded ceiling screens). 3/34 IC nurses or technicians had mild PSC changes.
Threshold dose (Conf intervals)	--
Prevalence at 1 Gy (95% CI)	--
Comments	Doses not known. Physicians were older than nurses/technicians. Study suggests that protracted radiation exposures may lead to opacities, but age needs to be ruled out.

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Author and date	**Hsieh et al., 2010**
Reference	Hsieh WA, Lin I-F, Chang WP, Chen W-L, Hsu YH, Chen M-S. Lens opacities in young individuals long after exposure to protracted low-dose-rate gamma radiation in 60Co-contaminated buildings in Taiwan. Radiat Res. 2010; 173:197-204. Chen W, Hwang J, Hu T, M C, Chang WP. Lenticular opacities in populations exposed to chronic low-dose-rate gamma radiation from radiocontaminated buildings in Taiwan. Radiat Res. 2001;156:71-77.
Type of study	Examination of opacity prevalence in cohort of those exposed to chronic gamma radiation in ^{60}Co contaminated residences
Number of individuals	73 persons under 20y of age when first examined in 1998. Now examined 4.7 y later. Comparison group of 100 healthy volunteers without exposure (ages 6-22 y)
Ages at exposure	Exposed for up to 15 y
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 15y)
Dose rate	Mean 7.4 ± 3.7 y of exposure
Technique for assessment	Slit-lamp examination after pupil dilation
Endpoints	LOCS-III assessment, plus Focal Lens Defects (FLD) to grade minor opacities (cf. Day et al., 1995)
Ages at observation	14.9 ± 3.8 y

Follow-up time	Exposures ceased from <1 to >5 y before the exam
Confounders evaluated?	Age, time since exposure ceased
Description of results	Found increase in FLDs between the 1st & 2nd exams & a significant (p=0.002) increase in FLDs in the exposed group. The exposure-associated increase in FLDs was found in the anterior cortex, but not the posterior cortex or nucleus.
Threshold dose (Conf intervals)	--
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.

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13264 **Japanese Atomic Bomb Studies**
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Author and date	**Cogan et al., 1950** **Cogan et al. 1949**
Reference	Cogan DG, Martin S, Kimura S. Atomic bomb cataracts. Science. 1949;110:654-655; Cogan DG, Martin SF, Kimura S, Ikui H. Ophthalmologic survey of atomic bomb survivors in Japan, 1949. Trans Am Ophthalmol Soc. 1950;48:63-87.
Type of study	Screening in 1949 (4 y after A-bomb exposure)
Number of individuals	1000 persons within 2000 m of hypocenter, 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	Exam 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	Largest percents were ages 16-20 y (18%) or 6-10 y (12%) in 1949; very few over age 60 y
Follow-up time	4 y
Confounders evaluated?	Other ocular findings noted

Description of results	No cases they considered “radiation cataract” in the 769 at 1000-2000 m. 81 lens abnormalities noted in the 231 at <1000 m, but none considered “unquestionable cases of radiation cataract”
Threshold dose (Conf intervals)	--
Prevalence at 1 Gy (95% CI)	--
Comments	Screening study 4y after A-bomb exposure. Their definition of “radiation cataract” may have excluded an unknown number of cases (e.g., 38 had cortical cataracts, some of which might have been radiation-related)

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Author and date	**(N) Nefzger et al., 1969;** **(O82) Otake & Schull, 1982;** **(O90) Otake & Schull, 1990;** **(O96) Otake et al., 1996**
Reference	(N) Nefzger MD, Miller RJ, Fujino T. Eye findings in atomic bomb survivors of Hiroshima and Nagasaki: 1963-1964. Am J Epidemiol. 1969;89:129-138. (O82) Otake M, Schull W. The relationship of gamma and neutron radiation to posterior lenticular opacities among atomic bomb survivors in Hiroshima and Nagasaki. Radiat Res 1982;92:574-95 (O90) Otake M, Schull W. Radiation-related posterior lenticular opacities in Hiroshima and Nagasaki atomic bomb survivors based on the DS86 dosimetry system. Radiat Res. 1990;121:3-13. (O96) Otake M, Neriishi K, Schull WJ. Cataract in atomic bomb survivors based on a threshold model and the occurrence of severe epilation. Radiat Res. 1996;146:339-348.
Type of study	Screening of a stratified random sample of A-bomb survivors
Number of individuals	(N) 2,468: 1,627 in Hiroshima, 841 in Nagasaki, examined in 1963-64 (O82) 2125 examined – 1394 in Hiroshima & 731 in Nagasaki (O90) – 1,983 with DS86 doses: 1325 in Hiroshima & 658 in Nagasaki (O96) – 1742 with DS86 doses & information on epilation
Ages at exposure	All ages, plus *in utero*; (O90) – *in utero* not included, since only 1 opacity case
Gender distribution	Not reported in either (N) or (O82)
Participation rate	~70%
Dose	Dose groups: (N) “High”= estimated dose >=200 rad (T-57 doses) or >=100 rad if in utero (n=1026); “Low”= within 2000m

	but <200 (or 100) rad (n=789); “Minimal”= 3000-9999m (n=388); Not in city (NIC, n=265); (O82) NIC=263; 0=264; 1-99 rad=627; 100-199=417; 200-399=368; 400-599=120; 600+=65; Unk=1. Group doses by 100 m distance only, estimated from preliminary DS86 using “free in air” doses times shielding factors of 0.9 in Hir. & 0.85 in Nag. (Shielding factors are now believed to be more like 0.4-0.7, so mean doses were likely overestimated.); (O90) – 71 of the 76 had DS86 doses. (O90 & O96) Used individual DS86 doses.
Radiation type	Gamma + neutron
Dose rate	Instantaneous
Technique for assessment	Ophthalmoscope (+ slit-lamp if ophthal. positive); examiners blinded as to dose but indicated that exposure information may have been communicated in interactions by examinees.
Endpoints	(N) Axial opacities, cortical opacities, nuclear opacities, polychromatic changes; only 84 axial opacities considered “radiation opacities”. About 70% were classified as "equivocal, minimal (<1mm) or small (1-2.4mm), the rest were "moderate" (~24%) or "large" (5 cases); (O90) – 71 cases used after review of records rejected some as not being PSC opacities & some with unknown dose
Ages at observation	17 y to over age 50 (not otherwise specified)
Follow-up time	18-19 y
Confounders evaluated?	(N) Not stated, other than age; (O82) In Hiroshima, those >100 rad were 3-4 y younger than those <100 rad; (O90) reported higher dose groups were of significantly older age. The participation rate was somewhat higher in the exposed groups than in those NIC or 0 dose. Questionnaire data indicated that participants were more concerned about their vision than nonparticipants.
Description of results	(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 & prenatal exposure. (O82) Based on re-review, accepted 76 axial opacities
Threshold dose (Conf intervals)	(N) Increased axial opacities seen only in high-dose group. They indicated that “new” T65 doses were 2-3 times lower for Hiroshima than their T-57 dose estimates, but little change was seen for Nagasaki dose estimates. (O82) Best-fit was a linear gamma—linear neutron with a likely T65D threshold of about 1.1 Gy (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). (O90) Best fit was a linear-gamma & 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 & 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 & 1.68 Sv) (O96) Once 35% individual dose uncertainty was factored in & using gamma + 10xneutron eye doses, the threshold estimates were 1.21 Sv for the epilation group & 1.41 Sv for the no-epilation group.
Prevalence at 1 Gy (95% CI)	--
Comments	(N) First cataract study of A-bomb survivors with reasonably good epidemiologic methods. Limited, and probably inaccurate, dosimetry; No individual dosimetry (N & O82), but used DS86 doses for (O90 & O96). (N) Unable to estimate separate gamma & neutron effects, whereas O82 & O90 did so. Opacity ascertainment was limited, because slit-lamp was used primarily when ophthalmoscopy was positive. (O90) Gamma & neutron are highly correlated, so attempting to estimate separate gamma & neutron effects is questionable, especially since it was based on only 71 opacity cases. Therefore the combined gamma-neutron dose threshold of about 1.4 Sv is probably more meaningful.

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Author and date	**Choshi et al., 1983**
Reference	(C) Choshi K, Takaku I, Mishima H, Takase T, Neriishi S, Finch S, Otake M. Ophthalmologic changes related to radiation exposure and age in Adult Health Study sample, Hiroshima and Nagasaki. Radiat Res. 1983;96:560-579. [1]
Type of study	Screening study of A-bomb cohort. Attempted to screen all with 100+ rad and an age-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: 84; postnatal 2301.
Ages at exposure	Exams 33-35 y after exposure. Ages from prenatal to 50+y
Gender distribution	62% females
Participation rate	Postnatal ATB, 47% of eligible; prenatal, 29%. Participation rate did not differ by dose.
Dose	(C) 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 as to dose group.
Endpoint	Primarily axial opacities; also examined PSC early changes
Ages at observation	181 (8%)<40y, 521(24%) 40-, 739(34%) 50-, 385(18%) 60-, 367(17%) 70+. Prenatal 32-34 y
Follow-up time	33-35 y
Confounders evaluated?	It was noted that there was substantial variability among the study ophthalmologists in scoring small axial opacities & PSC changes.
Description of results	There was an increase in axial opacities in the 100+ rad group for all age groups <70 y old. Overall, 26.1% in 100+ rad group & 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 (Conf intervals)	--
Prevalence at 1 Gy (95% CI)	--
Comments	Since they screened only those with 100+ rad & unexposed, no dose-response could be estimated. They used T65D dosimetry.

[1] Note: Otake et al (1992) reanalyzed 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 reanalysis is not included here. (Ref: Otake M, Finch S, Choshi K, Takaku I, Mishima H, Takase T. Radiation-related ophthalmological changes and aging among Hiroshima and Nagasaki A-bomb survivors: a reanalysis. Radiat Res. 1992;131:315-324)

Author and date	**(M) Minamoto et al., 2004;** **(N) Nakashima et al., 2006.**
Reference	(M) Minamoto A, Taniguchi H, Yoshitani N, Mukai S, Yokoyama T, Kumagami T, Tsuda Y, Mishima HK, Amemiya T, Nakashima E, Neriishi K, Hida A, Fujiwara S, Suzuki G, Akahoshi M. Cataract in atomic bomb survivors. Int J Radiat Biol. 2004;80:339-345. (N) Nakashima E, Neriishi K, Minamoto A. A reanalysis of atomic-bomb cataract data, 2000-2002: a threshold analysis. Health Phys. 2006;90:154-160.
Type of study	Screening study within the A-bomb Adult Health Study cohort
Number of individuals	(M) 873 persons; (N) 701 (postnatal exposed only); (numbers were limited because ophthalmologists were scheduled for only 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 ages 0-13y, 229 >13y (Mean= 8.8 y)
Gender distribution	61% females
Participation rate	93% examined
Dose	Mean= 0.52 Sv. Range= 0 to >2 Sv (DS02 dosimetry)
Radiation type	Gamma + neutron
Dose rate	Instantaneous
Technique for assessment	(M) Ophthalmoscopic & slit-lamp exam with pupil dilation, LOCS-II scores; exams by several examiners (& significant observer differences in PSC scoring were found, even though observer re-standardization was repeated every 6 mo. & reported agreement was consistently >80%); examiners blinded re: dose; obtained lens photographs; (N) Re-review of lens photographs by one ophthalmologist
Endpoints	Nuclear, cortical & PSC opacities
Ages at observation	54-94y. Mean=64.8 y
Follow-up time	55-57 y
Confounders evaluated?	Participation rate did not vary by radiation dose; evaluated 23 questionnaire variables & 15 laboratory measures for possible confounding; adjusted for city, sex, age, smoking
Description of results	Used proportional odds model (for graded responses), with adjustment for city, sex, age & 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 once can't 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 & smaller percentage with higher doses.
Threshold dose (Conf intervals)	(N) Cortical opacities, 0.6 Sv (<0, 1.2); PSC, 0.7 Sv (<0, 2.8) (these analyses excluded *in utero* exposed)
Prevalence at 1 Sv (95% CI)	(M) ORs for opacities & 95%CI: nuclear 1.12 (0.94, 1.30), cortical 1.29 (1.12, 1.49), PSC 1.41 (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 odds ratios. The initial study (M) had some problems with variations between examiners in scoring, but (N) had a uniform scoring by 1 examiner & the results were very similar. Note: This was the 1st A-bomb study to get away from classifying "axial opacities", which probably were a mixture of nuclear, cortical & PSC.

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Author and date	**Neriishi et al., 2007**
Reference	Neriishi K, Nakashima E, Minamoto A, Fujiwara S, Akahoshi M, Mishima HK, Kitaoka T, Shore RE. Postoperative cataract cases among atomic bomb survivors: radiation dose response and threshold. Radiat Res. 2007;168:404-408.
Type of study	Ophthalmoscopic examination to determine cataract surgery prevalence in Adult Health Study (AHS) cohort
Number of individuals	3761 who attended AHS during 2000-2002
Ages at exposure	0 to >20. 21% ages 0-10y, 48% 11-20y, 31% 21+y
Gender distribution	Not reported, but about 60% females
Participation rate	All who came to the AHS clinic (~70% of those eligible)
Dose	0 to >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 to 94 y
Follow-up time	55-57 y
Confounders evaluated?	Analyses adjusted for city, sex, age & diabetes mellitus
Description of results	479 (12.7%) persons with cataract surgery. Linear dose term was statistically 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 & restricted dose range). While there were age by sex & age by city interactions, there were none with radiation dose & the dose response was not affected.
Threshold dose (Conf intervals)	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 characterized. This is the first substantial evidence that radiation doses <1 Gy are related to clinically significant cataracts. Models assuming neutron RBEs of 5, 10, 15, 20 & 25 were examined. An RBE=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 cataract surgery incidence (1986-2005) also show a statistically significant dose association and a low dose threshold.)

APPENDIX B. MODELLING LOW LEVELS OF RISK OF RADIATION-INDUCED HEART DISEASE

(B 1) There are many uncertainties associated with estimating risks of radiation-induced heart disease, in particular at low levels of risk. Uncertainties include those associated with the volume of heart irradiated, the homogeneity of the dose, and the lack of knowledge of the most radiosensitive structures of the heart. Also, the relationship between the responses to acute, fractionated, or chronic irradiation is not known with reasonable accuracy. At low levels of risk, large datasets are required to detect significant differences between the study population and the controls, and this is compounded by the high natural rate of heart disease. Another important aspect is the follow-up time, because the risk of such late reactions keeps increasing with increasing observation time. Hence threshold doses are expected to be lower at long observation times.

(B 2) For circulatory disease, many estimates excess relative risk (ERR) in the literature from medical, occupational and other radiation exposure scenarios give estimates around 0.1 per Gy (for Sv see footnote) over a range of 0 to 4 Gy (Section 2). Specifically for mortality from heart disease, the aggregate mean value is 0.08 (AGIR, 2010). As the baseline rate for circulatory disease in developed countries is 30-50% of all deaths, the mean excess mortality from 0.5 Gy would be approximately 0.5x0.08x(30-50) = 1.2-2%. This is the main basis for choosing 0.5 Gy as the threshold dose, to give an excess mortality of the order of 1%. If the excess was linear with increasing dose, it follows that after 1, 2, 3 Gy the excess mortalities would be 3.2%, 6.4%, 9.6% respectively.

(B 3) One of the common ways in radiobiology to characterise dose-response slopes is to use a linear-quadratic (LQ) formulation based on Poisson statistics: NTCP = exp(-exp[lnK-(α+βd)D]), where NTCP is the normal tissue complication probability, α and β are coefficients of the linear and quadratic dose terms, lnK is a constant, D is the total dose, and d is the dose per fraction if the total dose is fractionated. If a single dose is used, d=D. Other terms can be added for low-dose-rate effects on β, and for cell repopulation, where appropriate. The ratio α/β in Gy is a measure of the sparing effect of dose fractionation, often called fractionation sensitivity, and α/β is the dose at which equal amounts of effect are produced by the α and β components. For late reactions a generic value of 3 Gy is commonly used for the α/β ratio. For the heart in rodents, a value of 3.7 Gy was calculated based on latency time before death, used as a surrogate endpoint for incidence. The value for human heart is unknown, except for a value of 2.5 Gy for early pericarditis. However, the relationship of this endpoint to late morbidity or mortality is unknown.

(B 4) If it is assumed that the excess risk at low doses can be described by α, and say α/β =3 Gy, then it follows that at 3 Gy the excess mortality could be 9.6% from the α component, and a further 9.6% from the β component making a total of 19.2%. Even at 2 Gy, there would be some contribution from the β component. This could help explain the trend towards an increase in excess risk with increasing dose (Carr et al 2005; Schulz-Hector and Trott, 2007). In the early days of the application of linear-quadratic modelling for fractionation effects, a “flexure dose” was defined at 1/10 of the α/β value, as the dose per fraction at which deviation from linearity

could be detected i.e. 0.3 Gy in this case (Fowler 1983, Tucker and Thames 1983). There was also an example of no further sparing for late reactions in the mouse kidney when the dose per fraction was reduced below even-higher values of 1-2 Gy (Stewart, 1987). This linearity at low doses per fraction could help explain the lack of change in a threshold dose of 0.5 Gy when an acute dose is replaced by a fractionated dose or a dose delivered at low dose rate, which reduces the β effect. This interpretation helps to underpin the conclusion that the threshold dose appears to be independent of fractionation (Section 4).

(B 5) It was shown that the data for heart disease incidence in acutely-exposed survivors of the atomic bombs, and in patients with peptic ulcer or breast cancer who had received fractionated dose radiotherapy, could be brought into reasonable agreement by normalising all the data to single-equivalent doses using the LQ model (Schulz-Hector and Trott, 2007). This showed a small threshold dose and a rising risk as the dose increased, compatible with the above considerations. This general agreement was not very dependent on the actual value of α/β chosen (AGIR, 2010).

(B 6) The peptic ulcer study is very informative because of the large number of 3719 patients involved, and of the 2936 deaths, 2187 were from causes other than cancer, including 1097 from circulatory diseases. The average follow-up duration was 22.5 years for irradiated and 27.5 years for non-irradiated patients. Also, in each of the 4 dose groups chosen, there were around 100 deaths for coronary heart disease. Daily fractions of 1.5 Gy were delivered to the stomach region to different total doses. Mean total in-field doses, delivered to about 5% of the heart (the apex), were 7.6, 10.6, 12.9, 18.4 Gy in the 4 dose groups chosen, and estimated mean heart doses were 1.6, 2.3, 2.8, 3.9 Gy. This indicates a mean dose per fraction of 0.32 Gy to the heart, and corresponding single-equivalent doses of 1.25, 1.64, 1.90, 2.40 Gy. In previous calculations (Schulz-Hector and Trott, 2007) an α/β ratio of 2 Gy was used, which would give slightly lower single-equivalent doses of 1.17, 1.52, 1.74, 2.17 Gy. Values of excess risk were 0, 23%, 54%, 51%. Hence, assuming an α/β ratio of (3-2) Gy, the risk per Gy at these doses would be 0, (14-15)%, (28-31)%, (21-24)%. The mean over the first 3 doses is (14-15)%, and over all 4 doses is (16-18)%. Carr et al (2005) were aware of the uncertainty of their dose estimates and subsequently performed a sensitivity analysis assuming a larger proportion (10% instead of 5%) of the heart in the field. This would have increased the total tissue-weighted dose by 24%, and raised the dose range slightly from 1.6-3.9 Gy to 1.9-4.8 Gy (Mabuchi et al 2006). Hence the values of risk per Gy would be decreased by 24%. The above values, and the trend towards an increase in risk per Gy with increasing dose, are compatible with the calculations above using LQ expectations. The values also support a threshold single dose of less than 1 Gy, deduced from the effects of these low fractionated doses.

(B 7) For breast cancer patients receiving radiotherapy, two large databases and reviews provided substantial information about the risk of circulatory disease. Paraphrasing this information from the review by Schulz-Hector and Trott (2007): in the total cohort of 308,861 women treated for early breast cancer between 1973 and 2001 and listed in the Surveillance, Epidemiology, and End-Results (SEER) cancer registries, 115,165 received postoperative radiotherapy as part of the primary treatment (Clarke et al 2005). Of those 4130 women who died more than 10 years after radiotherapy, 894 (22%) died from heart disease. The risk of death from heart disease was higher by 44% in women with left-sided compared right-sided breast cancer. In absolute numbers, 359 women with right-sided breast cancer and 535 women with left-sided breast cancer died from heart disease, which is an excess of

176 deaths of which 44 were due to myocardial infarction, 72 from other ischemic heart disease, and the remainder from other heart disease. The second large database is from the Early Breast Cancer Trialists' Collaborative Group (Paszat et al 1998, Darby et al 2005) on the cause-specific mortality among 20,000 women at 10-20 years after primary treatment involving adjuvant radiotherapy. There was a statistically significant increase (about 30%) in the annual death rate from cardiovascular deaths, which was ascribed to inadvertent irradiation of the coronary arteries, the carotid arteries, and other major arteries. These two large databases led to a general conclusion of an excess risk of 40-50% after a single-equivalent dose of 1.5 Gy, in broad agreement with the peptic ulcer study and the atomic bomb survivors (Schulz-Hector and Trott, 2007). Since that time, it was noted by Darby et al (2010) that a preliminary analysis of updated EBCTCG data had related mortality from heart disease to estimated cardiac doses in over 30,000 women followed for up to 20 years. There was clear evidence that the radiation-related increase was higher in trials with larger mean cardiac doses and that the risk of death from heart disease increased by 3% per Gy (95% CI, 2%-5%; $2p < 0.00001$) (Early Breast Cancer Trialists' Collaborative Group, 2007). That estimate could be taken only as an approximate indication of the risk, as individual treatment plans were not available for the women in those trials.

(B 8) There are also analyses of other clinical trial data for heart disease after radiotherapy of breast cancer and Hodgkin's lymphoma, using another dose-response model, which appear to have come to different conclusions compared to those above (Eriksson et al 2000; Gagliardi et al 1996, 2010). Dose-response curves were shown for cardiac mortality as a function of heart dose (calculated for the case of uniform irradiation of one third of the heart volume), indicating a 1% incidence level at about 27 Gy (2 Gy fractions) in breast cancer patients, and at about 24 Gy in Hodgkin's lymphoma patients (Figure B1).

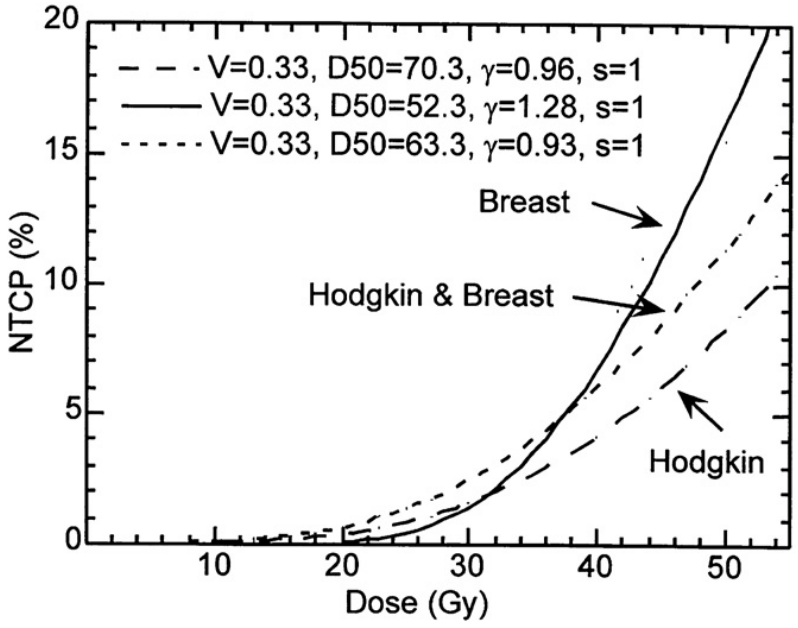

Figure B1. Dose–response curves for long-term cardiac mortality based on Hodgkin's disease and breast cancer data sets. Curves were obtained by fitting, respectively, Stockholm and Oslo breast cancer trials data and data from a patient cohort treated for Hodgkin's disease. Plotted curves correspond to a uniform irradiation of one third of the heart volume, in the interval of the clinical data (Eriksson et al. 2000).

(B 9) This led to recent recommendations (Gagliardi et al 2010) that "for partial heart irradiation, conservative (NTCP) model-based estimates predict that a heart volume of <10% exposed to 25 Gy (in 2 Gy fractions) will be associated with a <1% probability of cardiac mortality ~15 years after radiotherapy. For this prediction an overly-safe model was used that may overestimate the risk. Conversely, as the follow-up interval used is modest, this may underestimate the risk. For the vast majority of lymphoma patients who receive chemotherapy (particularly doxorubicin) and radiotherapy, it seems prudent to limit whole heart doses to ~15 Gy (in 2 Gy fractions) with field reductions, as appropriate in the given clinical situation, to areas of persistent (post-chemotherapy) residual tumour or to areas of previous bulky involvement." These doses are much higher than those being discussed above as threshold doses.

(B 10) In order to generate these numbers, the relative-seriality model was used together with dose-incidence data from radiotherapy trials in Oslo and Stockholm with breast cancer and Hodgkin's disease patients (Gagliardi et al 1996, 2010; Eriksson et al 2000). In the Stage 1 breast cancer trial in Oslo, 170 patients received radiotherapy versus 186 controls. There were 7 deaths from myocardial infarction in left-sided breast cancer patients, and 3 such deaths with right-sided. The excess mortality at 15 years was 7.9% for left-sided (95% confidence intervals 0.06 to 15%) and not significant for right-sided. Detailed dose-volume histograms were calculated, and normalised to 2 Gy per fraction assuming homogeneous radiosensitivity of the heart structures. By inspection of these using 20% quintile intervals, it can be calculated that the mean heart dose was about 20 Gy in 2 Gy fractions. Using $\alpha/\beta=3$ Gy, that translates into a single-equivalent dose of 8.6 Gy. Hence the excess risk would be only 1% per Gy, and less if there was a quadratic dose component. The risk would be higher if (1) incidence values nearer the upper 95% confidence limit were used (there were small numbers of events), (2) if the follow-up period had been more than 20 years e.g. Hooning et al (2006) reported hazard ratios in another series of 1.0 during the first 10 years of follow-up, 1.5 at 10–20 years, and 2.9 at more than 20 years after the start of treatment, and (3) if all deaths from ischaemic heart disease rather than solely myocardial infarction had been used (Gagliardi et al 1996). In the Stockholm breast cancer trial the mean excess risk was about the same but with even wider confidence intervals making it non-significant at the lower 95% limit.

(B 11) For Hodgkin's lymphoma (Ericksson et al 2000), 157 patients received mediastinal irradiation, with 69 of them (43%) prescribed 40 Gy in 2 Gy fractions, 58 (37%) prescribed 42 Gy, and the remaining 30 (20%) received doses either between 7 and 40 Gy or between 42 and 45 Gy. Hence the dose range for the majority of patients was small. Patients were grouped according to dose-volume constraints: group 1, 56 patients who received >38 Gy to 35% heart volume; group 2a, 51 patients who received <38 Gy to 35% volume and >35 Gy to 30% volume; group 2b, 36 patients who received <35 Gy to 30% volume. The excess risk at 15 years was 7.9, 5.5, and 3.8% in the three groups. Similar reasoning to the above for breast cancer treatments gives equivalent-single mean doses to the heart of about 10.8, 9.1, and 6.7 Gy in the 3 groups, and again leads to an excess risk per Gy of <1%.

(B 12) The relative-seriality model has parameters D50 (dose giving 50% complication probabilities (Gy), γ (the maximum relative slope of the sigmoid dose-response curve, being the maximum absolute increase in percentage complications

for a 1% increase in dose), and s (the relative-seriality factor). The values of γ were 1.28 (breast cancer patients) and 0.96 (Hodgkin's disease patients), which are at the low end of the range of 1 to 5 calculated for late reactions in various normal tissues and organs (Bentzen 2009). At a response level of 0.5, a γ_{50} of 1.0 corresponds to a γ_{05} of 0.05 (Bentzen 2007) i.e. at 5% incidence, the local slope of the sigmoid dose-response curve is 0.05% change in incidence per 1% change in dose. A 5% incidence of heart disease occurred after about 38 Gy in 2 Gy fractions for the breast cancer patients and about 42 Gy for the Hodgkin's lymphoma patients. Hence the excess risk per Gy (2Gy fractions) at the 5% incidence level would be 0.05/0.38 and 0.05/0.42, or just over 0.1% per Gy (2 Gy fractions), and less than this at lower incidence levels. Hence the modelled parameter values confirm the low values of excess risk per Gy at low incidence levels derived above from the raw patient numbers.

(B 13) 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 (like for cataracts), as is the case of the atomic bomb survivors (40-50 years follow-up e.g. Preston et al 2003, Yamada et al 2004, Shimizu et al 2010), and the peptic ulcer study (22.5 and 27.5 years, Carr et al 2005). 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.

(B 14)

Footnote: By ICRP convention, doses resulting in tissue reactions (deterministic effects) should be quoted in Gy or RBE-weighted dose RBE.D (Gy), rather than Sv which is reserved for clearly stochastic effects. The 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.D (Gy), may be used" (ICRP, 2007). It is recognised that 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 this cardiovascular endpoint remains uncertain. For low LET radiation, the actual numerical value in either unit is the same.

Appendix B References

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