The British Journal of Radiology, 82 (2009), 353–362

COMMENTARY

21st L H Gray Conference: the radiobiology/radiation protection interface

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ABSTRACT. The 21st L H Gray Conference, organised by the L H Gray Trust with the Society for Radiological Protection, brought together international experts in radiobiology, epidemiology and risk assessment, and scientists involved in diagnostic and therapeutic radiation exposure. The meeting — held in Edinburgh, Scotland, on 4–6 June 2008 — aimed to raise awareness, educate and share knowledge of important issues in radiation protection. A distinguished group of speakers discussed topics that included (i) non-targeted effects of radiation, (ii) exposure to high natural background radiation, (iii) non-cancer effects in Japanese bomb survivors, (iv) lessons learnt from Chernobyl, (v) radiation in the workplace, (vi) biokinetic modelling, (vii) uncertainties in risk estimation, (viii) issues in diagnostic medical exposures, (ix) lessons leant from the polonium-210 incidence and (x) how the radiobiology/radiation oncology community is needed to help society prepare for potential future acts of radiation terrorism. The conference highlighted the importance, relevance and topicality of radiobiology today.

Received 8 December 2008
Accepted 19 December 2008

DOI: 10.1259/bjr/8891994

The L H Gray Memorial Trust

The L H Gray Memorial Trust was set up in 1967 to honour the memory of Hal Gray, who made important contributions to the application of radiation physics to biology and medicine. The Trust was founded by the British Institute of Radiology, the Association for Radiation Research and the Hospital Physicists' Association (now the Institute of Physics and Engineering in Medicine). Since its formation, the Trust has organised a number of conferences and workshops on radiation effects, medical imaging and radiation protection. The 21st L H Gray Conference, organised by the L H Gray Trust with the Society for Radiological Protection, brought together international experts in radiobiology, epidemiology and risk assessment, and scientists involved in diagnostic and therapeutic radiation exposure. The meeting — held in Edinburgh, Scotland, on 4−6 June 2008 — aimed to raise awareness, educate and share knowledge of important issues in radiation protection. The conference highlighted the importance, relevance and topicality of radiobiology today.

Calculating risks from radiation exposure continues to be a subject of debate. The linear-no-threshold (LNT) dose–effect model is broadly accepted as representing the relationship between cancer incidence and dose. The model is the keystone of radiation protection, with risks being proportional to dose, and underlies the radiation protection principle of ''As Low As Reasonable Achievable'' (ALARA). Evidence for the LNT model comes from epidemiological studies using doses over 50 mSv, but its applicability at low doses is questioned. The field of radiobiology has developed rapidly over the past 5–10 years. Some radiobiologists believe that there is a threshold below which there is no increased risk of cancer with low linear energy transfer (LET) radiation. Several radiobiologists involved in studies of DNA repair genes have shown that defence mechanisms in cells activate following exposure to low doses of radiation. A threshold could arise from such an adaptive response, which could even provide a beneficial effect from low doses of radiation (radiation hormesis). However, there are also experimental data suggesting hypersensitivity to low doses of ionising radiation. The situation is, therefore, complicated and considerable work is required to gain a complete understanding.

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Radiobiology

Radiation-induced DNA damage response

The meeting started with an overview of how cells respond to DNA damage and how understanding this process has led to the identification of novel targets for the treatment of cancer (Steve Jackson, Cambridge). Over the past 20 years, it has become increasingly clear that

inherited or acquired mutations in genes involved in the detection, signalling and/or repair of DNA damage are associated with a range of human pathologies, including cancer. DNA is subject to a continual barrage of everyday oxidative stress. This endogenous damage is generally quick and easy to repair in an error-free manner. In contrast, radiation damage is associated with DNA double strand breaks (DSBs), which are very cytotoxic and often mis-repaired, *i.e.* they either kill a cell or make it genetically unstable. Understanding how cells respond to radiation damage is important because it should highlight novel targets not only for cancer therapy but also for the amelioration of, or protection from, radiation toxicity. ATM (ataxia-telangiectasia mutated) and ATR (ATM and RAD3-related) protein kinases are central sensors and regulators of the DNA damage response and act by signalling to control cell-cycle transitions, DNA replication, DNA repair and apoptosis. DNA-PK (DNA-dependent protein kinase) is one of the key enzymes involved in DNA DSB repair. It is activated by DNA DSBs, facilitates the alignment of the two broken ends of the DNA molecule and coordinates recruitment of other factors to the repair complex.

The ~2 m of DNA in a human cell is condensed by wrapping around scaffolding proteins to form chromatin. One of the histone proteins involved in this DNA condensation, H2AX (H2A histone family, member X), is phosphorylated in the presence of DSBs to generate γH2AX. Phosphorylation of H2AX by ATM, ATR or DNA-PK leads to the recruitment of DNA damage response proteins following irradiation. These proteins target an overlapping set of substrates, with ATR being essential for the viability of replicating cells and ATM and DNA-PK functioning in response to DSBs. Formation of a DSB leads to the recruitment of the MRN complex (meiotic recombination protein-11 (MRE11)–RAD50–Nijmegen breakage syndrome protein-1 (NBS1)) and the separation of the dimeric inactive form of ATM to a monomeric phosphorylated form. This monomeric form of ATM binds the MRN complex at the DSB and is further activated by the DNA and MRN complex. Activated ATM then phosphorylates H2AX. γH2AX binds to MDC-1 (mediator of DNA damage checkpoint protein-1), leading to recruitment of additional ATM–MRN complexes and further H2AX phosphorylation. The activated ATM also phosphorylates downstream targets, including Chk2, which leads to cell-cycle arrest. There are two main pathways of DSB repair: homologous recombination and non-homologous end-joining (NHEJ). Homologous recombination occurs in proliferating cells and involves ATR activation. NHEJ occurs in quiescent cells and involves DNA-PK.

Increased understanding of the DNA damage response has led to the development of new drugs aimed at inhibiting their effects in cancer cells. A key rationale underlying the development of these drugs is that tumour cells already have defects in some DNA damage repair pathways, making them more susceptible to inhibition of another pathway. Inhibitors of PARP1 (poly(ADP-ribose)polymerase), which binds to damaged DNA and facilitates single-strand break repair, are very effective at killing cells that are already unable to repair DNA via homologous recombination, such as cells with mutations in *BRCA1* or *BRCA2*, which are common in some cancers. The PARP inhibitor AZD2281 is well tolerated in cancer patients and very promising early results have been seen in a Phase I trial.

Non-targeted effects of ionising radiation and radiation risk assessment

Arguably, the most important development in recent years in our understanding of the biological effects of ionising radiation comes from observations of non-targeted effects. Bill Morgan (University of Maryland) summarised our current understanding of these effects and their implications for radiation protection. Non-targeted effects are seen in non-irradiated cells, *i.e.* either the progeny (radiation-induced genomic instability) or non-irradiated neighbours (bystander effects) of irradiated cells. The importance of these effects for radiation protection lies in understanding the scientific basis for protecting the public from exposures to very low levels of ionising radiation (<0.1 Sv) where there are considerable uncertainties in epidemiological data. Low doses of ionising radiation might be more harmful than thought from the extrapolation of high-dose epidemiology data, with supralinearity at low doses and higher risks than indicated from the LNT model. This supralinearity could arise from low-dose hypersensitivity, genomic instability and detrimental bystander effects. There is evidence for the occurrence of these effects i*n vitro* and *in vivo* but they are not seen in all cells or tissues. Responses include changes in gene and protein expression, induction of mutations, chromosomal aberrations, transformation and cell death, and there is evidence for the involvement of secreted cytokines. Abscopal effects — a reaction produced following irradiation occurring outside the field of radiation absorption — have also been observed in experimental animals and humans.

There is evidence not only for effects that might lead to supralinearity of the low-dose region of the dose–response curve for cancer induction but also for less than linear adaptive responses — radiation hormesis. Complex biological systems have physiological barriers against damage and disease and some people believe that low-dose stimulation of DNA repair processes is beneficial. The issues surrounding the new biology of non-targeted effects include (i) the demonstration of these effects predominantly *in vitro* and not in all cells, (ii) the unknown relationship between genomic instability and carcinogenesis, (iii) the unknown relative biological effects for high LET radiation, and (iv) how non-targeted effects might be modified by individual and tissue susceptibilities. All these areas require further study, and thus the risks from low-level ionising radiation exposure are uncertain.

Adaptive response in radiation risk

Ron Mitchel (AECL, Chalk River, Canada) discussed adaptive responses to low LET radiation in more detail, highlighting how the LNT model is *assumed* to be true for all humans, organisms and tissues. However, exposure to mild stress, including low doses of radiation, induces a defensive adaptive response in virtually every type of

cell and organism examined, including human cells. The response to low-dose radiation is part of a general stress response, and other stressors can modify radiation risk and *vice versa*. The main protective mechanisms induced following low-dose irradiation are DNA repair, apoptosis and immune surveillance. A low dose of radiation can produce a variety of protective outcomes: induction of DNA repair and resistance of cells to a second dose of radiation; increased sensitivity for radiation-induced apoptosis (protective because it leads to elimination of damaged cells); and protection of cells against neoplastic transformation by high doses of radiation. Most importantly, a low dose alone, in the absence of a second high dose, will reduce the frequency of neoplastic transformation in mouse and human cells to a level below that of the spontaneous frequency in unexposed cells, *i.e.* provide an absolute reduction in risk. The protective effects seen *in vitro* are also seen *in vivo.* For example, a single low dose/low dose-rate exposure given before a large exposure increased the latency of leukaemia development and the lifespan of irradiated mice. However, as *in vitro*, a single low dose/low dose-rate exposure alone *in vivo* produced an absolute reduction in risk below that of the spontaneous risk of unexposed mice by increasing the latency of a variety of spontaneous cancers, thereby increasing the lifespan of the mouse. *In vivo,* tissue-specific upper-dose thresholds are observed, above which protection gives way to detriment. Protection by radiation against chemically induced tumour initiation and tumour formation in mice has also been seen. All of these *in vitro* and *in vivo* protective effects are dependent upon the functional activity of *TP53*; reduced *TP53* function modifies both the magnitude of the protection and the tissue-specific upper-dose thresholds, underlining the importance of individual genetic variation for risk estimation. There are a number of implications of these observations of adaptive responses for radiological protection. Firstly, high-dose responses cannot be extrapolated to low doses, and dose thresholds for increased risk exist. Secondly, if some doses are protective, radiation dose risks are not additive, as currently assumed. Thirdly, the dose and dose-rate effectiveness factor (DDREF) used in radiation protection might be wrong. If the risk from low dose/dose-rate exposure is ≤ 0, then the DDREF is actually infinity, rather than the value of 2 recommended by the International Commission on Radiological Protection (ICRP). Fourthly, tissue-weighting factors used for radiation protection (w_T, see below), which are assumed to be constant and dose independent, are actually dose dependent and, at least for some tissues, will decrease to negative values as doses decrease below the upper-dose threshold for protective effects in those tissues. Fifthly, as the risk of low doses of low LET radiation is <0, radiation-weighting factors for high LET radiation (w_R, which represent the ratio of risk between high and low LET exposures) have no meaning at low doses of radiation. Sixthly, the ALARA concept might prevent an exposure that would induce a beneficial adaptive response and *increase* risk. Although, it is too soon to change the current radiation protection system, it is clear that further research in this area is important for future modification of the LNT model so that it properly reflects actual responses from low doses.

Exposure to multiple stressors

Carmel Mothersill (McMaster University, Canada) highlighted that pollutants are seldom present in the environment as single agents. This generally unresearched area is potentially important for radiation protection because different risks might occur depending on the background exposure to factors other than radiation. Multiple stressor doses of chemicals are added together to determine risks, but it remains to be established whether additive risks for radiation plus chemical doses can be assumed. Limited data from old studies suggest a maximum impact with low doses of radiation, with both hormetic and synergistic interactions occurring. There are also limited data suggesting that chemicals can induce non-targeted adaptive and bystander responses. There is a clear need for experimental data with mixed contaminates to increase our mechanistic understanding and aid consequence modelling. It is also important to be aware that background genetic and epigenetic effects will be important.

Two examples of potential complex scenarios were presented. First, radiation induces a cell to undergo apoptosis, thus removing it from the potentially carcinogenic pool. A pollutant metal interferes with the signalling cascade and the cell survives. Although a survival assay suggests protection, the cell is likely to be genomically unstable. Second, radiation induces an adaptive response in a cell and a further stress has no effect. Another cell not previously irradiated is killed by the same stressor. These possibilities raise the issue that risks might also be dependent on prior exposure to the same or a different stressor. For example, a population from a high background radiation or polluted area might have responded adaptively and be protected against additional exposure to the same or another stressor. Different risk factors, therefore, might be required for populations living in polluted *vs* pristine environments when exposed to radiation. Although the current approach to risk assessment — dose driven, mono-agent and mainly mutation centred — ignores low-dose exposure data available for radiation and the issue of multiple stressors, it is clear that further research is vital to increase our understanding of this area.

Epidemiological studies

Estimates of the risks to health that occur following exposure to ionising radiation underpin radiological protection, and are obtained from epidemiological studies of suitably exposed groups of humans. These exposed groups include the Japanese atomic bomb survivors, environmentally exposed populations (*e.g.* those living in areas of high natural background radiation; Chernobyl), occupationally exposed individuals and medically exposed groups.

Exposure to high natural background radiation: what can it teach us about radiation risk?

The main source of human exposure to ionising radiation comes from the environment, with the largest

contribution from radon. Jolyon Hendry (IAEA, Vienna; Manchester) provided an overview of radiation risk estimates from human exposure to natural background radiation. People who live in high natural background areas of the world are of considerable interest because they and their ancestors have been exposed to abnormally high radiation levels over many generations. In Ramsar, Iran, approximately 2000 people receive ~10 mGy per year and a lifetime exposure of 650 mSv. The highest recorded doses are ~250 mGy per year. However, despite extensive knowledge of radiation risks gained through epidemiological investigations and mechanistic considerations, the health effects of chronic low-level radiation exposure remain poorly understood. The need was highlighted for detailed consideration of study design to adequately power epidemiological investigations and for analysis of chromosomal aberrations in the blood of people living in high natural background radiation areas (Guarapari, Brazil; Kerala, India; Ramsar, Iran; Yangjiang, China), including radon-prone areas. Informative studies exist only for radon and lung cancer risks, which provide a convincing association between long-term protracted radiation exposures in the general population and disease incidence. The success of studies showing an association is due to tissue doses being elevated and large-scale collaborative studies being conducted, with careful individual reconstruction of exposures and collection of information on potential confounding factors. Steps taken in China and India, including the establishment of cohort and case-control studies, provide a model framework for the assessment of low-dose risks from high background radiation and could be used as a model in other areas of the world.

Cancer and non-cancer effects in Japanese bomb survivors

Mark Little (Imperial College, London) highlighted the importance of studying Japanese bomb survivors for estimating the risk of low radiation doses/dose-rates in the UK. The study of other groups, such as medically exposed individuals and workers in the nuclear industry, generally has insufficient power to make meaningful conclusions and can be limited in terms of population age and gender. Latest analyses suggest a large upward curvature for the risk of leukaemia increasing with radiation dose and a more modest upward curvature for solid cancers. The UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) 2006 mortality and incidence models show similar cancer risks to other recent estimates (BEIR (National Academy of Sciences Committee on the Biologic Effects of Ionizing Radiation) VII, ICRP 2007). These latter risks are lower than previous estimates (UNSCEAR 2000), predominantly because of a change in the models used to calculate risks (see ''Biokinetic and dosimetric models'') and to a lesser extent because of a revised calculation of atomic bomb dosimetry. The risk of developing cancer in atomic bomb survivors appears to be higher than for patients who underwent radiotherapy (particularly leukaemia), an observation attributed to the higher doses received by the latter group resulting in cell death rather than transformation. However, recent analyses, which have accounted for different radiation doses to bone marrow compartments, suggest no differences in radiation-induced cancer risks between atomic bomb and medically irradiated individuals. Epidemiological studies have also investigated the risk of developing non-cancer disease from radiation exposure. Excess risks of various types of non-malignant conditions in the Japanese atomic bomb survivors, in particular cardiovascular, respiratory and digestive diseases, are similar, suggesting a possible systematic bias in the data. In support of this idea, radiation-associated respiratory and digestive diseases have not been seen in other groups — radiotherapy patients and Chernobyl recovery workers. Although cardiovascular risks have been reported, in contrast to cancer, there is less consistency in risk estimates between studies and no reliable conclusions can be drawn.

Chernobyl: what have we learnt from it?

22 years following the Chernobyl accident, Elisabeth Cardis (CREAL, Barcelona) summarised the lessons learnt about its effect on health. The main exposed populations were the liquidators (~240 000; mean effective dose of 100 mSv), the 1986 evacuees (~116 000; mean effective dose of 33 mSv) and people living in contaminated areas (~270 000, mean effective dose of 50 mSv; ~5 million, mean effective dose of 10 mSv). An increased risk of developing thyroid cancer has been shown with nearly 5000 cases among those who were younger than 18 years of age at the time of the accident and 4000 among those who were under 15 years. The increased risk has been confirmed in several epidemiological studies. However, the prognosis of those developing thyroid cancers is good, with only 15 deaths recorded up to 2006 among those exposed in childhood. There is also evidence for the risk being higher in those with iodine deficiency and lower in those who took dietary iodine supplements. There remains uncertainty regarding the pattern of risk over time but there is likely to be an increased risk for many years. The effect of exposure as an adult also remains unclear. There has been no increase in risk clearly demonstrated yet for the development of other cancers but there are suggestions of possible increases in leukaemia and other malignancies among liquidators, and of breast cancer in young women in the most contaminated districts. Leukaemia, associated with radiation exposure in atomic bomb survivors and other exposed populations, is often considered a ''marker'' of radiation effect. Leukaemia develops early, usually 2−14 years following irradiation. Results of studies in those exposed *in utero* or in childhood are inconclusive but are limited owing to inadequate statistical power. A twofold increased risk of leukaemia was reported in highly exposed liquidators. Other studies in exposed populations also suggest an increased risk but a firm conclusion remains difficult to make because of limited statistical power and also a lack of information on other potentially more important risk factors (*e.g.* tobacco and alcohol) and radiation doses. Therefore, although ionising radiation is associated with an increased risk of many types of cancer in atomic bomb survivors and other exposed populations, there is no firm evidence for any increase (except for thyroid cancer)

in those exposed as a result of the Chernobyl accident. However, radiation-induced solid cancers can develop decades after exposure and it is too early to fully evaluate the full radiological impact of Chernobyl on cancer induction.

There are also no clearly demonstrated increases in the incidence of other diseases that can be attributed to radiation exposure following the accident. Other potential health effects include cataracts, cardiovascular diseases, immunological system effects, heritable effects, birth defects, and mental, psychological and nervous system effects. Possible effects have been reported on the risks of cataracts and cardiovascular diseases. Cataracts have long been known to occur at high doses and studies of liquidators suggest they may also occur at lower doses (0.25 Gy). Early liquidators who suffered acute radiation syndrome are likely to have an increased risk of cardiovascular disease and there are reports of increased mortality in Russian liquidators. Of course, the lack of demonstrated increased risk does not mean that there is no risk, and all of these cancer and non-cancer effects require further investigation. Based on experience of other populations, small increases in the relative risk for cancer and other diseases are expected and studies to date have suffered from low statistical power and methodological limitations. Although predictions based on other populations are uncertain, they provide an estimate of the order of magnitude of the possible risk. Careful studies are now required to study the real effect, as it is clear that the true impact on health of the accident has not been studied comprehensively. There is a need for coordination to develop a consensus on the impact, feasibility and usefulness of studies. Such coordination has the potential to provide answers to some of the current questions in radiation protection. The development of a comprehensive long-term strategic research agenda by the Agenda for Research on Chernobyl Health (ARCH) should address these issues by coordinating a comprehensive long-term research agenda.

Radiation in the workplace

Richard Wakeford (University of Manchester) gave an overview of lessons learnt from studies of occupationally exposed populations. Such work provides an important check on the risk estimates underlying radiological protection and may be the only opportunity to investigate risks for some radionuclides. Workplace exposed groups also enable the effects of protracted exposure to low doses of ionising radiation to be studied. The work involves radiologists/radiographers, underground hard rock miners (inhalation of radon and its radioactive decay products), radium dial painters, air crew and nuclear industry workers.

Epidemiological studies of radiologists and radiographers in various countries have shown an elevated risk of leukaemia and some evidence for a radiation risk for breast and skin cancers. These data are predominantly for people exposed in the first half of the 20th century when radiation exposures were high; however, the lack of individual dose records prevents definitive conclusions. To date, there is no clear evidence of an increased cancer risk in medical radiation workers exposed to current levels of radiation doses. Air crew are exposed to elevated levels of cosmic radiation, but studies have not revealed any radiation-related risks. Radium dial painters and radium chemists — exposed to radium-226 (^{226}Ra) and ^{228}Ra — had an increased risk of bone and paranasal sinus cancers but no evidence for an excess risk of leukaemia. Underground hard rock (*e.g.* uranium, iron, gold and tin) miners have been exposed to high lung doses in the past. A clear excess of lung cancer was demonstrated, enabling definitive risk estimates to be obtained for lung cancer following radon exposure, which is consistent with the results of case–control studies of residential exposure. There is, however, little evidence for a risk of other cancers.

Nuclear industry workers generally have the best dosimetry records available but, as average doses are low, large studies are required for statistical power. As the nuclear industry was established in the 1940s, workforce studies are only just reaching maturity. A three-country study involving ~95 000 radiation workers with an average follow-up of 22 years suggested an excess relative risk (ERR)/Sv of ~2 for leukaemia but no increased risk for any other cancers. The recently published 15-country study included ~400 000 workers with an average follow-up of 13 years. An ERR/Sv of ~2 was seen for leukaemia and lung cancer; the ERR was ~1 for all cancers. However, a confounding effect from smoking has been suggested to be partly responsible for the increased risk of non-leukaemia cancers, and the Canadian data give anomalously high results. Workers in the Mayak nuclear weapons complex in Russia were exposed to high levels of external radiation and plutonium, especially before 1959. An ERR/Gy of ~8 was seen for leukaemia with external radiation exposure. No increase in leukaemia was seen with plutonium exposure, which was associated with an elevated risk of lung, liver and bone cancers. International collaboration will be useful to study risks from internal emitters.

Biokinetic and dosimetric models

The ICRP framework for estimating radiation risks is dominated by epidemiological data from populations exposed to external radiation. The ICRP, therefore, developed biokinetic and dosimetric models that enable calculation of the macroscopic distributions of radiation in organs and tissues following inhalation or ingestion of a wide range of radionuclides. The models are used to calculate equivalent and effective dose coefficients (dose per Bq intake) for occupational and environmental exposures. Dose coefficients are also given for a range of radiopharmaceuticals used in diagnostic medicine. Using equivalent and effective dose, exposures from external sources and from different radionuclides can be summed for comparison with dose limits, constraints and reference levels that relate to risks from whole-body radiation exposure.

Biokinetic modelling and risk

Biokinetic modelling for the estimation of radiation risks was the subject of a talk by John Harrison (Heath

Protection Agency). The various models (*e.g.* respiratory tract, systemic) consider the transfer of radionuclides to multiple organs and tissue compartments following inhalation or ingestion. There are different models for different radionuclides and age at intake is taken into account (*e.g.* adult, child, foetus). For example, the human respiratory tract model includes extrathoracic (nasal, oropharynx, larynx) and thoracic (bronchi, bronchioles, alveolar interstitial) compartments. They consider the transfer, retention and excretion of radionuclides and distribution within organs relative to target tissue. Dosimetric models are used to convert exposure to dose, taking account of the type of radiation. Radiation (w_R) and tissue (w_T) weighting factors have been defined by the ICRP for use in the calculation of equivalent and effective dose for radiation purposes. For example, a w_R of 1 is used for all low LET radiations and a w_R of 20 is used for α-particles for all cancer types. These weighting factors are used so that the absorbed dose (Gy) can be converted to an equivalent dose to individual tissues (Gy $\times$ w_R = Sv), which can then be summed to give an effective dose to the whole body in Sv (sum of equivalent doses to radiosensitive tissues $\times$ w_T). Effective dose is a radiation protection devise used for regulatory purposes, which allows summation of external and internal exposures with very different organ/tissue doses and time-courses of dose delivery. w_T values are age- and gender-averaged. For the first time, phantoms will be published by the ICRP for the separate calculation of equivalent doses to males and females; these will be averaged in the calculation of effective dose.

Biokinetic and dosimetric models are validated and improved by fitting data from exposed individuals. The increasing sophistication of some of the new models is probably greater than required for regulatory control purposes. However, they are also used to calculate best estimates of doses and risks to individuals in epidemiological studies and to determine the probability of cancer causation. Models are then adjusted to best fit the characteristics of the individuals and population under consideration. For example, doses resulting from the release of strontium-90 (^{90}Sr) and other radionuclides to the Techa River from the Russian Mayak plutonium plant are being estimated using models adapted to take account of measurements on local residents and other population-specific data.

It is important to recognise there are uncertainties in risk estimates (see below). Although the ICRP is the main source of biokinetic and dosimetric models, others are available. For example, a revised systemic model for polonium, used in the calculation of doses during the London polonium-210 (^{210}Po) incident, has not yet been adopted by the ICRP. The models undergo continual refinement, improvement and development. Application in the protection system must, therefore, continually be aware of the best current science.

Uncertainty in risk estimates

ICRP dose coefficients are published as single values without consideration of uncertainties, which were discussed by Dudley Goodhead. The assessed cancer risks have tended to increase over the decades and dose limits have been successively reduced. The ICRP 103 report published in 2008 recommends annual dose limits of 20 mSv for occupationally exposed individuals and 1 mSv for the general adult population. Although radiation risks are much better quantified compared with other environmental toxins, new data continue to emerge for differences in the type (*e.g.* non-cancer) and quantity of risk. For radiation protection, limits are set in terms of effective or equivalent dose as surrogates for whole-body/tissue risks. A complicated but crude system is used to achieve additivity of risk from all exposures. The system is convenient for rough planning purposes in radiological protection but only provides ball park estimates. Examples of uncertainty in estimated coefficients for cancer risk per unit dose for external low-LET radiation are a factor of ~8 overall for fatal cancers estimated in the National Council on Radiation Protection and Measurements (NCRP) 126 report and a factor of ~5 in the ICRP99 estimates of risk of cancer incidence. Risk estimates are complicated by different types of radiation and routes of exposure. Uncertainty in estimating risk is greater for internal emitters than for external radiation because of uncertainties in biokinetics and dosimetry. Uncertainty is element/radionuclide dependent and is, for example, small for hydrogen-3 (^{3}H), iodine-131 (^{131}I) and caesium-137 (^{137}Cs) but large for plutonium-239 (^{239}Pu). Larger uncertainty factors will be seen for individual organs and cancers. For example, uncertainty in risk estimates for ^{90}Sr after lung inhalation is in the 1000s. Other uncertainty factors for internal emitters have been reported: ~5 for ^{137}Cs (all tissues); ~8 for ^{131}I (thyroid) and~30 for ^{90}Sr (bone surface, marrow). Of course, these uncertainties are in addition to uncertainties in risk coefficients per unit dose and in intake (route, amount and form of each radionuclide). Published risk estimates do not indicate uncertainties and so may be misleading.

Each new version of the ICRP framework introduces a variety of additional uncertainties to the overall estimation of risk. For several classes of internal emitters, however, average dose may not be adequate to describe the heterogeneity of microscopic energy deposition within an organ. The problem is most relevant to radionuclides that emit short-ranged radiations, such as α- and β-particles and auger electrons. In principle, such issues may arise in any situation for which the spatial distribution of the internal emitter is non-uniform (non-random) relative to the distribution of the target cells, or tissue components, on a scale of the ranges of the emitted radiations. The problem may be compounded by the higher LET of the short-ranged radiations.

Developments in radiation oncology and implications for radiation protection

Kate Vallis (Gray Institute of Radiation Oncology and Biology, Oxford) overviewed some of the recent developments in radiation oncology. The change from 20th century empirical to 21st century targeted therapy was highlighted. These developments include increased targeting of the delivery of external beam radiation to tumours (physical optimisation), molecular targeting to enhance the radiosensitivity of tumour cells (biological optimisation) and tumour-specific targeting with radio-

nuclides. Some of the radiation protection issues surrounding the potential risk of carcinogenesis with increased physical optimisation are discussed later (see ''IMRT, protons and secondary cancers''). Knowledge of developments in biological targeting are relevant, as there is a need to understand and model the potential risks associated with the systemic delivery of radiotherapy involving a variety of radionuclides and targeting agents.

An example of biological optimisation involving targeted therapy is the use of epidermal growth factor receptor (EGFR) antagonists. EGFR is expressed on the surface of epithelial cells but can be expressed at much higher levels on many solid tumour cells. The receptor is stimulated following growth factor binding, which initiates a signalling cascade within cells that leads to increased tumour cell proliferation, de-differentiation and survival (protection from apoptosis), and promotion of angiogenesis. The use of EGFR antagonists has been shown to increase radiosensitivity and the response of tumours to radiotherapy. The increase in survival seen when the anti-EGFR antibody cetuximab is combined with radiotherapy has spurred further research in the area and the development of radiolabelled conjugates of the receptor binding EGF. Not all cells respond to anti-EGFR approaches. For example, tumours that have mutated *KRAS* appear to be resistant, an observation that raises the issue of defining and targeting other/multiple cell signalling pathways relevant for radiation survival. Another potential target of interest in radiotherapy is Akt, which is a central signalling molecule in cells. Promising clinical results have been seen with the farnesyltransferase inhibitor nelfinivir, an HIV protease inhibitor that leads to dephosphorylation of Akt protein and sensitisation of cells to radiation.

Tumour targeting with radionuclides is an expanding area of research and the radioimmunotherapy (yttrium-90 (^{90}Y)-ibritumomab) of non-Hodgkin's lymphoma has become the standard of care for recurrent or relapsed disease. Another example of a radionuclide targeted therapy being investigated clinically is indium-111 (^{111}In)-EGF. As the ^{111}In radionuclide emits both γ radiation and auger electrons (only toxic in close proximity to DNA and so nuclear translocation is important), it is useful for both imaging and treatment, respectively. The radiolabelled EGF targets cells over-expressing EGFR specifically and has potent activity *in vivo*. The biological targeted therapy carried out to date shows how we are beginning to understand the characteristics of a molecular target, which are likely to make it useful for radiosensitisation or for radionuclide therapy. It is clear that agents that target these processes can be taken into the clinic to alter outcome. Their increasing use in the clinic means that there is likely to be a future need for biokinetic and biodosimetric models for the new radionuclide therapies, and issues of radiological protection will need to be addressed.

Issues in radiation practice

Issues in diagnostic medical exposures

Medical exposures comprise ~14% of background radiation in the UK, but this value is increasing with the rising number of imaging investigations carried out (Alex Elliott, Glasgow). For example, the number of CT scans carried out increased from 1 709 244 in 1995 to 2 728 119 in 2006. In the US, medical radiation exposure currently contributes ~50% of the total background doses, with ~67 million CT scans carried out in 2006, giving a *per capita* dose of 1.45 mSv. The latest faster and high-resolution scanners are used with an increasing range of indications and as a tool for screening asymptomatic patients. There has been a rapid emergence of private companies offering whole-body CT scanning as a health check-up.

In the UK, the government's advisory committee on the health effects of natural and man-made radiation in the environment is the Committee on Medical Aspects of Radiation in the Environment (COMARE). The COMARE Medical Practices Subcommittee recently produced a report (COMARE 12) on the impact of personally initiated X-ray CT scanning for the health assessment of asymptomatic individuals. The report made a number of conclusions: (i) there is a non-trivial risk associated with certain CT examinations; (ii) there is a significant incidence of false-positive findings, which may lead to further (over)investigation and anxiety; and (iii) for diseases with a low prevalence, individuals may suffer more detriment than derive benefit. The subcommittee's recommendations included: (i) the need to provide comprehensive and consistent information regarding eligibility, dose and risk of CT scans; and (ii) the lack of justification for several of the applications being promoted such as whole-body CT scanning of asymptomatic individuals.

It is also important to be aware that there will be continued growth of medical exposure to ionising radiation. Nuclear medicine procedures are increasing rapidly, in particular the use of PET/CT scanners. The various radiotracers used with PET are associated with effective doses of ~3–11 mSv, which is in addition to the dose of ~6 mSv from the CT component. Questions that need to be addressed concerning radiation protection and diagnostic medical imaging include whether the LNT model and current values of relative biological effectiveness (RBE) are applicable to internally deposited radionuclides and whether there are particular groups more at risk than others. There is also a need to increase our understanding of the potential effects of non-ionising radiation, such as ultraviolet, electric and magnetic field (EMF) and ultrasound.

Mammography — oncogenicity at low doses

Geoff Heyes (University Hospital Birmingham) highlighted the controversy surrounding the RBE of low energy X-rays used for mammography breast screening. Recent radiobiological studies showed that the low-energy X-rays used in mammography may be ~4 times more effective in causing mutations than higher energy X-rays. Data were presented showing that, for women in the UK NHS breast-screening programme, the benefit safely exceeds the risk of possible cancer induction even if the RBE is four. However, the risk/benefit analysis for regular mammography starting at 20 years, 30 years or 40 years suggests a questionable benefit of screening

younger women. The potential risk of cancer induction is particularly high for those with a family history of (and therefore a likely genetic susceptibility to) breast cancer.

Radiobiological *in vitro* data are generally acquired at high doses and there are various extrapolation mechanisms to the low doses used clinically — linear and J-shaped (adaptive responses). Recent low-dose *in vitro* data indicate a potential suppressive effect at very low dose-rates and doses and a J-shaped response. However, recent epidemiological data of cancer risk in children and adolescents who underwent frequent X-ray examinations for spinal curvature continue to support the LNT model. Although not universal, most committees continue to propose the use of the LNT model.

Recent studies have shown that MRI is more sensitive than mammography at detecting invasive breast cancer in women with a genetic susceptibility. As an increase in the risk associated with mammography reduces the justification of exposure for this population, MRI and other (non-ionising) screening modalities should be used.

Implications of the bystander effect for radiotherapy

Bystander effects might have potential beneficial or detrimental effects in the clinic (Alastair Munro; Ninewells Hospital, Dundee). Advantages would be increased cell kill of tumour stem cells, elimination of adjacent pre-malignant cells, differentiation of undifferentiated cells, increased normal cell proliferation, increased radioresistance in adapted normal cells and rapid relief of symptoms. Potential disadvantages would be increased second malignancies, acute and late toxicity, radioresistance of adapted tumour cells and systemic effects. The issue of whether we will ever discover what implications bystander effects might have for radiotherapy was raised. A clarification was given of the generally synonymously used terms ''complicated'' and ''complex''. Complicated refers to a system that is not simple — having many interconnected parts — that is ultimately understandable. In contrast, complex refers to something that might be simple or complicated but has just too many interacting variables, which behave erratically, to be ever fully understood. This clarification then raised the issue of whether bystander effects in radiotherapy are complicated — and ultimately knowable and exploitable — or complex, in which case we will never fully understand them and will have a limited ability to exploit them. The same of course can be applied to clarifying the risks from low-dose ionising radiation exposure — are low-dose effects complicated and ultimately understandable or just too complex for us ever to be able to modify risk estimates away from the LNT model and ALARA principle? What is clear, however, is that further research is required before we can make any conclusions. Towards this goal, contributions from clinicians might include meticulous longitudinal studies involving multiple samples and analyses of chemical species, genomics, transcriptomics and proteomics.

IMRT, protons and secondary cancers

Bleddyn Jones (Gray Institute of Radiation Oncology and Biology, Oxford) discussed recent technical developments in radiotherapy. These developments are dominated by the change from the use of standard coplanar rectangular fields to conformal radiotherapy involving shaped fields. More recently, conformal treatments include intensity-modulated radiotherapy (IMRT), which involves non-uniform fluence across beams to reduce the doses to designated normal tissues with the goal of reducing late toxicity. IMRT leads to a larger total body dose owing to leakage radiation and, because of the use of more fields, a bigger volume of normal tissue exposed to low doses. An important radiation protection issue surrounding the move to IMRT is whether the low dose ''bath'' effect might increase the risk of secondary cancers. Some countries are also investing heavily into charged particles — protons and/or carbon ions — with sharp Bragg peaks that reduce integral doses by a factor of 2–10 and should also reduce the incidence of late toxicity and potential carcinogenesis (for caveat, see ''Is There a Place for Quantitative Risk Assessment?'').

A problem associated with calculating the risks of carcinogenesis following radiotherapy is that current risk estimates are based on large single-fraction dose exposures (atomic bomb survivors). There is a need to derive dose–response curves that include dose–time–fractionation and RBE effects. It will be useful in the future to include malignant induction probability (MIP) mapping on clinical dose distribution plans for patients with a high probability of long-term survival. Standard linear radioprotection models show a 2- to 15-fold reduction in risk with charged particle therapy depending on the treatment location. Using the linear quadratic (LQ) model, however, allows estimation of relative changes in carcinogenesis that incorporate fractionation and RBE effects. Using the LQ model, the classical turnover points in carcinogenesis (when risk plateaus before decreasing owing to cell death rather than induction of mutation) following single radiation doses become pseudolinear with fractionated doses, and there is an inverse relationship between dose per fraction and cancer induction. The turnover point indicates the dose at which risk is greatest and is highly dependent on fractionation and radiosensitivity.

The MIP is highly dependent on dose fractionation but potentially useful in guiding the choice of therapy/treatment planning technique. Considerable work is required before MIP is mapped onto treatment plans. There is a need for experimental studies that test the various modelling approaches using cellular malignant induction assays, simulation of IMRT and proton/ion beams in tissue-equivalent human phantoms and careful collection of clinical data sets using each radiation technique.

Radiation terrorism: what have we learnt from ^{210}Po?

Many useful lessons were learnt from the poisoning of Alexander Litvinenko with ^{210}Po in November 2006 in how to prepare for possible future acts of radiation

terrorism. Nick Gent overviewed the work of the Health Protection Agency (HPA), an independent body that protects the health and wellbeing of people in the UK. One of the three main centres of the HPA is Radiation, Chemical and Environmental Hazards, which includes the Radiation Protection Division (formerly the National Radiological Protection Board). The role of the HPA includes: (i) preventing further exposure of the public, (ii) assessing risks to those potentially exposed, (iii) identifying and caring for those requiring medical follow-up, and (iv) reassuring the public. Alexander Litvinenko was poisoned and admitted to hospital early in November, but a radiation injury was not confirmed until the end of the month. ^{210}Po decays by emission of α-particles, has a half-life of 138 days and is eliminated from the body via faeces, urine and perspiration.

The Litvinenko case tested and proved the ability of the UK to screen a large number of people (*e.g.* ~700 24 h urine samples were tested to measure dose exposures) and a complicated environment in a major city (*e.g.* involving hotels, taxis, restaurants and a football stadium). It also proved the value of the UK's existing well-established emergency planning and coordination arrangements, and illustrated the country's ability to coordinate and synergise with police and public health investigations. Although a single individual was poisoned, the incident affected over 1400 people in 49 countries.

The case usefully uncovered the need to (i) validate common approaches to the radiological protection of the public and occupational groups responding to such incidents; (ii) train health care professionals to recognise unusual illnesses; and (iii) learn how to marshal and use the extensive community of radiation professionals available in the UK.

Radiation terrorism: what society needs from the radiobiology/radiation oncology community

Norman Coleman (National Cancer Institute, Maryland, USA) presented his opinions on what society needs from the radiobiology/radiation oncology community. In the US, the Office of Assistant Secretary for Preparedness and Response (ASPR) is the government's body for preparing and dealing with bioterrorism. ASPR comprises four offices, of which the Biomedical Advanced Research and Development Authority (BARDA) is responsible for coordinating and advising on public health medical countermeasures via its Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). Potential acts of radiological terrorism include industrial sabotage, use of explosive or non-explosive radiological dispersal devices, placement of a radiological exposure device in a public facility and the use of an improvised nuclear device. The different types of potential event are associated with different features (*e.g.* from immediately to slowly recognisable as an event) and consequences (*e.g.* small or large number of mass casualties), but long-term monitoring is likely to be required for victims and responders.

The management of acute radiation syndromes depends on the dose received: haematological (>2 Gy), gastrointestinal (>6 Gy) and central nervous system (>10 Gy). The ASPR has developed a detailed chain of medical responses, which includes a radiation triage, transport and treatment system. They have mapped over 100 hospitals across the US with burn bed capacity and centres capable of dealing with the treatment of radiation injury. It is clear that multidisciplinary expertise is required for a comprehensive medical response to an act of radiological terrorism. It is also clear that the continued development and refinement of medical response plans requires scientists who can define, prioritise and address the gaps in our knowledge. Society needs radiation physics, radiobiology and radiation oncology expertise to (i) increase our understanding of radiation risks, (ii) improve methods for estimating radiation exposure *in vivo*, (iii) develop methods for protection from, and amelioration of, radiation damage and (iv) improve the management of exposed individuals. It also needs such expertise to communicate with and educate the community to improve their preparedness. The US government is investing in the development of medical countermeasures, rapid techniques for assessing exposure and basic research in mechanisms of radiation injury. The prospect of radiation terrorism is opening up new avenues for research at the radiobiology/radiation protection interface, which need exploiting to help develop effective responses.

Is there a place for quantitative risk assessment?

Eric Hall (Columbia University, New York, USA) stressed the need for quantitative risk assessment. Ionising radiation is an established part of life, which is associated with both fear (nuclear power) and indifference (diagnostic X-rays). The non-uniform reaction to the potential risks of radiation exposure highlights the importance of quantitative risk estimates, which are necessary to improve the public's perception of risks from radiation. Three areas were discussed where quantitative risk estimates are needed and where uncertainties and limitations are a problem: IMRT, protons and diagnostic X-rays.

The atomic bomb survivor data show that radiation-induced cancers appear at the same age as spontaneous cancers, and the estimation of solid cancer risks takes more than 50 years to complete. The data show that the ERR per Gy for a person aged 70 years exposed at age 30 years is ~1.3 for bladder cancer compared with ~0.3 for liver cancer. In general, it is difficult to estimate the risk of developing a second cancer following radiotherapy because of the lack of control data. The exceptions are for prostate and cervix carcinomas, where surgery is an option, and Hodgkin's disease, where the risk of breast cancer in young women is obvious. There is evidence for an increased risk of radiation-induced cancer for IMRT compared with conventional radiotherapy (*e.g.* 3% per Sv *vs* 1.5% per Sv after radiotherapy for prostate cancer). In older patients, such a doubling of second cancer incidence might be acceptable if balanced by an improvement in local tumour control and reduced toxicity. It might not be acceptable, however, in children where the radiation-induced second cancer incidence rate is much higher. It is important to be aware of potential methods to mitigate the problem: increased

shielding, secondary beam blocking, removing the flattening filter and using protons rather than X-rays.

Although, as stated above (in ''IMRT, protons and secondary cancers''), protons *should* eliminate the problem of radiation-induced cancers outside the treatment volume because of the reduction in the volume of normal tissues exposed, most facilities use passive scattering, rather than spot scanning, to spread the pencil beam to cover realistic target volumes. This process, together with the methods used for final collimation, result in substantial total body doses of neutrons, which have an estimated (assumed) RBE of 20–30. The solutions to this problem were presented: use a scanning beam and avoid the problems of passive modulation (technically difficult) or replace the brass collimator with one made of polyethylene or a hybrid made of both. The uncertainty surrounding the RBE of these neutrons highlights the need for further research in the area in order to improve risk estimates.

The rapid rise in CT usage over the past 25 years was highlighted again (see ''Issues in Diagnostic Medical Exposures''). At the present time, the organ doses from a study involving 2 or 3 CT scans is around 30−40 mSv, a dose where there is evidence of excess cancer risk in epidemiological studies. No extrapolation is required in this scenario to calculate risks and so the key question is: what is the lowest radiation dose at which we have solid data of an elevated cancer incidence? Data were presented showing a significant elevated risk for cancer mortality in atomic bomb survivors exposed to a mean dose of 0.035 Gy/5−125 mSv and for nuclear works exposed to an average cumulative dose of 0.02 Gy/19 mSv. In order to estimate risk, it was suggested to (i) calculate (estimate)/measure dose to each organ as a function of age, gender and type of CT scan, (ii) to apply estimates of age-, gender- and organ-specific risks per unit dose and (iii) to sum the risks for all organs. Using this approach, there was an estimated increased lifetime attributable all cancer mortality risk for individuals given a head CT before 25 years and for those given an abdominal CT before 35 years of age. Of course, risks must be considered in the light of potential benefits and, while scanning asymptomatic patients is not justified, a 1 in 1000 risk of developing a cancer following an abdominal CT scan is acceptable if the risk of not scanning is greater.

Summary

The LNT model and ALARA principle will provide the basis of radiological protection for the near future. There are too many uncertainties surrounding the influence of the new radiobiology — bystander effects, adaptive response, genomic instability — to know whether and in what situations (which radiation type, tissue, individuals) they can be applied. What emerged from the meeting was an overriding sense of how complicated the underlying issue of radiation risk assessment is. So many factors are involved: dose level, dose rate, acute *vs* chronic exposure, radiation type/radionuclide, route of exposure, tissues exposed, difference in genetic susceptibility, and interactions between stressors. The uncertainties — along with the need to plan for potential future acts of radiation terrorism and understand the health risks associated with technological development in radiotherapy and the increased use of radiation in diagnostic imaging — highlighted the importance for further research and funding for basic radiobiology.

Acknowledgments

The conference was supported by the UK Department of Health, the Scottish Government and Office of Science (BER), US Department of Energy, Grant No. DE-FG02-08ER64543. Individual speakers were sponsored by Cancer Research UK, the International Atomic Energy Agency, the Association for International Cancer Research, the British Association for Cancer Research and the UK Medical Research Council.