(b) Studies in exposed animals

Fission neutrons were reported to induce germ-line mutations in mice, including visible dominant mutations (Batchelor *et al.*, 1966), dominant lethal mutations (Grahn *et al.*, 1979, 1984, 1986), visible recessive mutations (Russell, 1965, 1972), and specific locus mutations (Russell, 1967; Cattanach, 1971). Neutrons have also been shown to induce *Hprt* mutations in splenic lymphocytes of mice (Kataoka *et al.*, 1993). Point mutations in K-*Ras* and N-*Ras* oncogenes were found in malignant tissue from mice exposed to neutrons, but the mutations could not be directly ascribed to the exposure (Zhang & Woloschak, 1998). Sister chromatid exchange was induced in bone-marrow cells of young rats exposed to fission neutrons (Poncy *et al.*, 1988), while micronuclei and chromosomal aberrations were observed in splenocytes of mice exposed to neutrons *in vivo* (Darroudi *et al.*, 1992). Reciprocal translocations were induced in stem-cell spermatogonia of rhesus monkeys exposed to neutrons (van Buul, 1989). In all these experiments, the fission neutrons were many-fold more effective, on the basis of absorbed dose, than sparsely ionizing radiation.

(c) Studies in cultured cells

DNA breaks induced by fast neutrons in L5178Y mouse lymphoma cells were classified into three types on the basis of their repair profiles: rapidly repaired breaks (half-time, 3–5 minutes), slowly repaired breaks (half-time, 70 minutes), and non-repaired breaks. Neutrons induced less of the rapidly repaired damage, a nearly equal amount of slowly repaired damage, and more non-repaired damage when compared with equal doses of X- or γ-radiation (Sakai *et al.*, 1987).

In mammalian cells, neutrons were more efficient than the same absorbed dose of X-rays or γ-rays at inducing gene mutation and chromosomal aberrations (Fabry *et al.*, 1985; Roberts & Holt, 1985; Hei *et al.*, 1988; Nakamura & Sawada, 1988; Kronenberg & Little, 1989; Kronenberg, 1991), and transformation (Balcer-Kubiczek *et al.*, 1988: Miller *et al.*, 1989; Komatsu *et al.*, 1993). In addition, extensive measurements of the induction of chromosomal aberrations (dicentrics or dicentric plus centric rings) in human lymphocytes as a function of the neutron energy have been performed (Lloyd *et al.*, 1976; Sevan'kaev *et al.*, 1979; Edwards, 1999; Schmid *et al.*, 2003).

4.4 Synthesis

- The energy-deposition characteristics of all sources of ionizing radiation are relatively well understood.
- All types of ionizing radiation, including neutron radiation, transfer their energy to biological material in clusters of ionization and excitation events, primarily through a free-electron-mediated mechanism.
- In cells, energy deposition from all types of ionizing radiation results in a wide variety of molecular damage; in DNA, this includes base damage and single- and double-strand breaks, some of which may be clustered and form complex lesions. Subsequent processing of these lesions may lead to chromosomal aberrations and mutations.
- Much evidence points to damage to DNA being of primary importance in the biological outcome of exposure to ionizing radiation, particularly the loss of cellular ability to form clones. It is generally assumed that the same DNA damage leads to tumorigenesis, and there is some evidence to support this.
- How the cell processes the initially produced damage to DNA to yield tumours is unknown; although many hypotheses have been the subject of research, few have gained wide consensus.

- Genome-wide sequencing of tumours has shown wide heterogeneity in constituent mutations, indicating there may be multiple pathways to tumour formation.
- Tumours produced after exposure to ionizing radiation have not been shown to carry any characteristic molecular markers.
- There is emerging consensus that epigenetic factors are important in tumorigenic processes. Notably, radiation induces effects such as genomic instability and bystander effects, which are epigenetic in origin.
- Also important are the interactions at the tissue level between radiation-damaged cells and normal cells, which may serve to modulate the effects of radiation. In addition, host factors such as age, gender, changes in immune status, telomere dysfunction, and genetic variations in specific genes may play a role, as well as modulation of gene expression.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of X-radiation and of γ-radiation. X-radiation and γ-radiation cause cancer of the salivary gland, oesophagus, stomach, colon, lung, bone, basal cell of the skin, female breast, kidney, urinary bladder, brain and CNS, thyroid, and leukaemia (excluding chronic lymphocytic leukaemia). Also, positive associations have been observed between X-radiation and γ-radiation and cancer of the rectum, liver, pancreas, ovary, and prostate, and non-Hodgkin lymphoma and multiple myeloma.

In-utero exposure to X-radiation and γ-radiation causes cancer.

There is *sufficient evidence* in experimental animals for the carcinogenicity of X-radiation and of γ-radiation.

X-radiation and γ-radiation are *carcinogenic to humans (Group 1).*

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