

RADIATION AND CANCER 2009

Molecular Oncology
Michael Lea
Michael Lea

RADIATION AND CANCER - LECTURE OUTLINE

1. Types of radiation
2. Irradiation of water
3. Radiation-induced cancer
4. Radiation toxicity
5. Radiation therapy
6. Radioprotectors
7. DNA repair

Types of Radiation

There are 2 types of radiation to be considered: electromagnetic and particulate. Electromagnetic radiation has energy but no mass. This includes X rays, gamma rays and ultraviolet radiation. Particulate radiation has both energy and mass and includes electrons, neutrons and alpha particles.

X rays arise from outside the atomic nucleus. They may be produced in vacuum tubes by accelerated electrons colliding with a solid body such as tungsten. Gamma rays arise from radioactive decay. They originate within the nucleus. The energies of X rays and gamma rays can overlap but in general gamma rays have higher energies. Ultraviolet radiation has a wavelength between 10 and 400 nm. Cosmic radiation consists of protons (79%), alpha particles (20%) and assorted atomic nuclei (1%).

Ionizing radiation includes alpha particles, beta particles (electrons), neutrons, X rays and gamma radiation.

The linear energy transfer (LET) is equal to the energy lost per unit track length. It is highest for alpha particles and lowest for gamma rays.

Alpha particles are less penetrating and most of the energy is dissipated in a short distance.

High LET radiation produces greater biological damage than low LET radiation and the ratio of doses to give the same biological effect is known as the relative biological effectiveness (RBE).

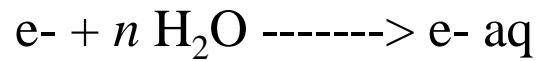
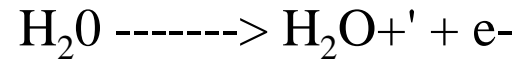
Units

The roentgen is the unit of exposure dose for X rays and gamma rays. The unit of absorbed dose is the gray (Gy) which is equal to 1 joule per kg of material such as tissue. The rad is an older unit and is equal to 0.01 Gy. The rem is the roentgen equivalent in man. The dose in grays differs for different types of radiation. Each type of radiation has different biological effects. The rem is equal to the dose in rads (cGy) x a quality factor (RBE).

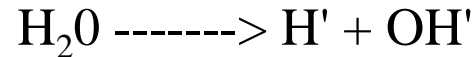
IRRADIATION OF WATER

Living cells consist largely of water and when they are irradiated it is the effects on water that create most of the ionization. Hydrated electrons, hydrogen atoms and hydroxyl radicals can be generated as follows:

Radiation



Radiation



IRRADIATION OF WATER

Hydroxyl radicals and hydrated electrons are the two major radicals resulting from the ionization of water. Hydroxyl radicals and hydrogen atoms can react with organic molecules by abstraction:



or by addition at olefinic and aromatic centers to form organic free radicals:



Hydrated electrons react by nucleophilic addition to form radical anions .

The main reactions of the organic radicals are dimerization, dismutation, oxidation and reduction. Reaction with molecular oxygen to form organic peroxy radicals would prevent restitution that can occur through reduction by a thiol compound.

RADIATION-INDUCED CANCER

The induction of cancer by radiation is dose dependent and high LET radiation is generally more effective than low LET radiation.

Tissues vary in their sensitivity to radiation-induced cancer. Bone marrow and the thyroid gland are highly sensitive. Breast and lung are moderately sensitive and lower sensitivity is seen in skin, bone, stomach and pancreas. Skin cancer occurred in some early workers with radioactive materials. After X ray treatment, the excess mortality from leukemia has been seen between three and eight years but for other types of cancer the excess mortality was maximal between nine and twenty years.

RADIATION-INDUCED CANCER

Evidence for the carcinogenic effect of ionizing irradiation in humans has come from observations on radium dial painters, radiologists, patients treated with irradiation for therapeutic purposes and from the survivors of atomic bomb explosions. However, for the general population the greatest single risk of radiation exposure may be in the induction of skin cancer by ultraviolet radiation in sunlight. The most carcinogenic wavelengths are between 290 and 340 nm. The formation of thymine dimers in DNA may be an important source of somatic mutations induced by ultraviolet light.

RADIATION-INDUCED CANCER

Thymine bases can also be affected by ionizing radiation. Free radicals react predominantly at the 5,6 double bond leading either to the formation of thymine glycols or to the opening of the thymine ring. The hydroxyl radical abstracts hydrogen from all available positions on deoxyribose which can lead to strand breaks in DNA. Both single and double strand breaks can occur. There may be some protection of DNA by associated proteins in chromosomes. Replicating DNA is more sensitive to the effects of ionizing radiation.

RADIUM DIAL PAINTERS OF NEW JERSEY

Between 1917 and 1924 about a thousand people were employed in the radium dial painting industry in New Jersey, principally in West Orange. The radioluminous dial paint contained radioactive isotopes (radium 226, radium 228 and thorium 228). The paint was applied with a brush and the workers frequently used their lips to get a fine point on the brushes. Early pathology noted in some of the workers included jaw necrosis and anemia.

In 1928, Harrison Martland reported the case of a young woman who died with both an osteogenic sarcoma and aplastic anemia. At autopsy her skeleton contained about 50 micrograms of radioactive material. Martland was the first to conclude that there was a causal relationship between skeletal deposits of alpha-particle-emitting natural radio-isotopes and the development of a specific tumor.

Reference: W.S. Sharpe, Academy of Medicine of New Jersey Bulletin 16: 55-62, 1970.

RADON

Radon is a chemically inert gas produced by the radioactive decay of uranium. The immediate decay products of radon are chemically reactive metals (polonium, bismuth, and lead) that tend to be retained in the lung when inhaled. The polonium decay products emit highly ionizing alpha particles. Studies of underground miners, animals, and dosimetry modeling have shown that radon decay products are lung carcinogens. In particular, epidemiologic studies of miners have shown a strong and consistent dose-response relationship between lung cancer and radon exposure.

(CDC Editorial Note 10/27/89)

Radon is believed to be the second leading cause of lung cancer. Indoor levels of radiation exceeding 4 picocuries per liter are considered to require remediation. In New Jersey the highest levels are found in the northwest of the state and the lowest levels are found in the south east.

ULTRAVIOLET RADIATION AND SKIN CANCER

“The ultraviolet component of sunlight is the major environmental agent that precipitates the clinical symptoms of skin carcinogenesis. This is well-established for squamous and basal cell cancers, but is still controversial for melanoma. Nonmelanoma skin cancers are by far the most common cancers that occur in the United States each year, comprising 30 to 40% of all cancers. The incidence is increasing at an alarming rate, and melanoma may be considered a quiet twentieth century epidemic.”

Cleaver and Mitchell (2003)

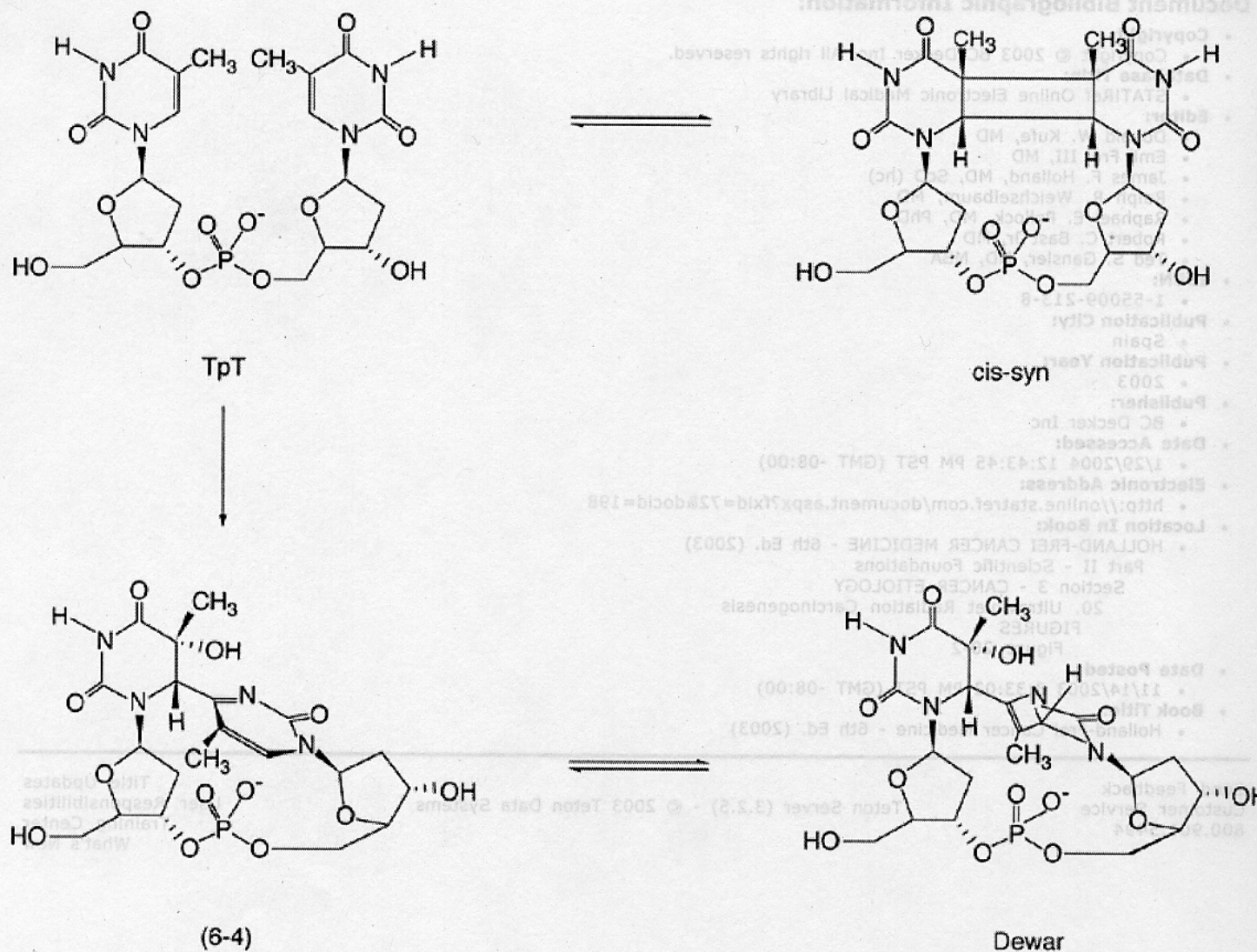


Figure 20-2 Photochemical reactions in a dipyrimidine DNA sequence leading to the formation of CPDs (TpT1, TpT2) or a (6-4)PDs (TpT4) and its photolytic derivative, the Dewar pyrimidine (TpT3). (Redrawn from Taylor and Cohrs.³⁵)

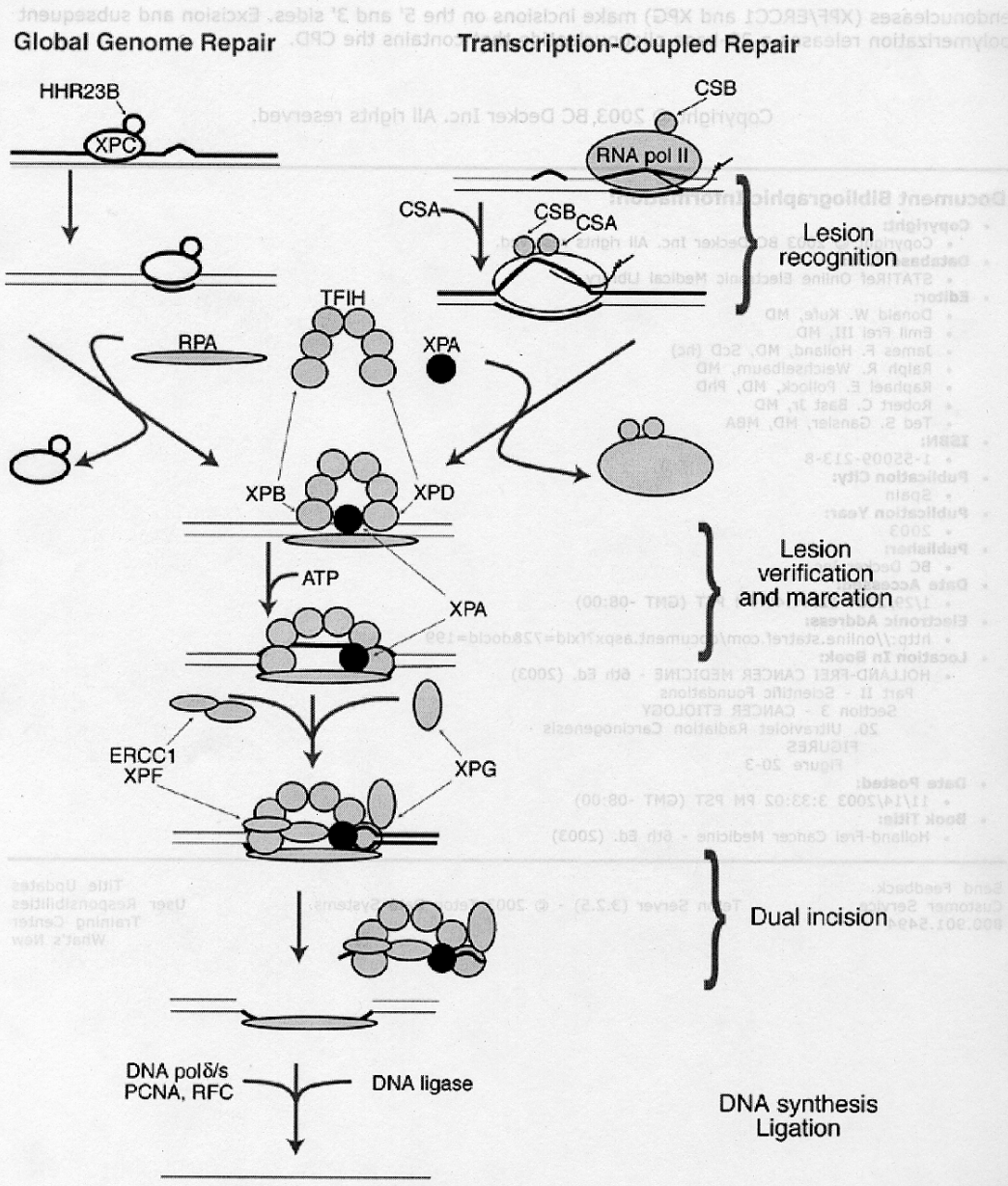


Figure 20-3 Biochemical steps for nucleotide excision repair of CPDs. Initial recognition of damage involves the XPC and E gene products, followed by XPA and RPA that bind to photoproducts and download the helicases XPB and D for local unwinding. Excision occurs when UV-specific

RADIATION TOXICITY

Human and experimental cancer induction curves for irradiation show variability in shape. Linear or curvilinear responses at lower radiation levels tend to plateau or show peak responses at higher radiation levels. Cell killing becomes a factor at the higher radiation levels. With whole body irradiation the critical tissue target is related to the dose. After 100-150 Gy, death occurs in hours from central nervous system damage. After 5-12 Gy, death follows in days from effects on the gastrointestinal tract, and after 2.5-5 Gy there is bone marrow toxicity which is fatal within a few weeks. Tissues may survive local irradiation at these levels because there can be repopulation of stem cells from unirradiated areas.

During the cell cycle, cells are most sensitive to irradiation in mitosis and again at the G1/S interface. They are least sensitive in mid G1 and in mid S

Table 19-3. Risks of Death from Various Activities^a

<u>Activity</u> (per million/year)	<u>Risk of Death</u>
Being a person age 55 years (all causes)	10,000
Smoking a pack of cigarettes daily (all causes)	3,500
Rock climbing for 2 h (accident)	500
Canoeing for 20 h (drowning)	200
Motorcycling for 1,000 miles (accident)	200
Traveling 1,500 miles by car (accident)	40
Being a pedestrian (accident)	40
Working 1 week as a firefighter (accident)	15
Working 1 week in agriculture (accident)	10
Fishing (drowning)	10
Eating (choking on aspirated food)	8
Skiing for 10 h (accident)	8
Working 1 month in a typical factory (accident)	5
Traveling 5,000 miles by air (accident)	5
Having a chest radiograph (radiation-induced cancer)	1
Visiting Denver for 2 months (cancer from cosmic rays)	1
Living in the vicinity of a nuclear power plant (radiation-induced cancer)	< 0.1

^a Estimates derived from various sources.

RADIATION THERAPY

Although cancer can be induced by radiation, there is an important role for radiation in cancer therapy. Accurate localization is essential in order to reduce toxicity in normal tissues. Several factors influence cell killing:

1. Dose rate

A fractionated dose reduces toxicity. The kinetics of recovery from sublethal damage may favor normal cells and permit repopulation of stem cells.

RADIATION THERAPY

2. Oxygenation

Cells with oxygen tensions above 30 mm Hg are 2-3 times more sensitive to X rays and gamma rays than cells at very low oxygen tensions. Tumors tend to have more hypoxic cells than normal tissues. Fractionation of the dose may permit shrinking of the tumor and recruitment of hypoxic cells into the well oxygenated cell fraction. There have been attempts to sensitize hypoxic tumor cells. Hyperbaric oxygen has been of limited value. Misonidazole is a drug which increases the radiation sensitivity of hypoxic cells. Agents which deplete cellular thiols, or inhibit DNA repair or react with DNA radicals to form unreparable species will sensitize cells to irradiation.

3. Radiation Quality

At a given dose, high LET radiation causes greater cell killing than low LET radiation. Hence neutrons will cause greater lethality than X rays and gamma rays.

4. RADIOPROTECTORS

The observation that cysteine increases survival after total body X-irradiation led to the search for agents which would be selectively protective for normal tissues. Cysteine can be cytotoxic for normal and tumor cells at high dose levels. More selective radioprotective agents have been identified which have phosphorothioate structures, notably WR-2721 which is S-2-(3-amino-propylamino)ethyl phosphorothioic acid. Preferential uptake in normal tissues may be a factor in the differential effect but this is not seen in all tumors. WR-2721 is not without toxic effects. It has some hypotensive action which may be secondary to ganglionic blocking activity.

5. DNA REPAIR

The importance of DNA repair mechanisms in recovering from sublethal radiation damage is suggested by the increased incidence of cancer in hereditary conditions which involve DNA repair defects. These include Xeroderma pigmentosum in which there is a defect in the repair of damage by ultraviolet radiation and there is a high incidence of skin cancer. In Ataxia telangiectasia there is hypersensitivity to ionizing radiation with an associated high incidence of leukemia, lymphomas, brain tumors and carcinomas of the stomach.

5. DNA REPAIR

Single strand breaks may be repaired by excision repair in which bases are removed by endonuclease activity and gap filling is achieved with DNA polymerase followed by ligation. Damaged bases can be removed by DNA glycosylase activity to create an apurinic or apyrimidinic site which will be subject to excision repair. Double strand breaks may sometimes require recombination with homologous undamaged DNA. It is important that DNA damage be repaired before mitosis and acquisition of a mutation by daughter cells. More rapidly proliferating cells are thus at greater risk from the effects of irradiation. The nucleoside analog 5-bromodeoxyuridine is incorporated into DNA and makes cells more sensitive to radiation.

5. DNA REPAIR

When DNA is damaged there is an increase in the activity of the enzyme poly (ADPribose) polymerase. There is conflicting data for the significance of this activity in DNA repair but in some systems inhibitors of poly(ADPribose) polymerase such as benzamide derivatives can potentiate the cell killing by irradiation.

SUGGESTED READING

1. H.C. Pitot. Fundamentals of Oncology, 4th ed., pages 86-93, 2002.
2. **J.B. Little. Ionizing Radiation in Holland-Frei Cancer Medicine (6th edition) Part II Scientific Foundations, Section 3 - Cancer Etiology, 19. Ionizing Radiation (2003).**
3. **J.E. Cleaver and D.L. Mitchell. Ultraviolet Radiation Carcinogenesis in Holland-Frei Cancer Medicine (6th edition) Part II Scientific Foundations, Section 3 - Cancer Etiology, 20. Ultraviolet Radiation Carcinogenesis (2003).**