Acute Hypoxia

Can develop in tumours when blood vessels are temporarily closed or blocked.

There is evidence that the blood vessels in tumours open and close in a random fashion so that different parts of the tumour become hypoxic intermittently.

As a result, some cells may be hypoxic during a radiation dose, but if the radiation is delayed a different group of cells may become hypoxic.

Acute Hypoxia is due to transient closure of capillaries or arterioles servicing parts of the tumour.

While this vessel is closed, the tumour cells become hypoxic and resistant to the indirect action of radiation.

These vessels are usually only closed for short times but may occur during a fractionated dose of radiation.

Splitting the dose into fractions raises the possibility of the closed vessel being open the next time around, and therefore allowing the tumour cells to be killed.

Clinical Applications

Clinical Use of the α/β Ratio

The α/β ratio provides the dose in Gray where cell killing from linear and quadratic components of the linear quadratic equation are equal. At points below this value, linear cell kill is dominant; in those after quadratic cell kill takes over. This ratio may be used in many areas of radiotherapy.

Differentiating early and late responding normal tissue

Clinical Applications (cont)

Early responding tissues (high α/β ratio) sensitive to total dose but with minimal effect with fractionation. Late responding tissues (low α/β ratio), demonstrating increased survival at low doses and significantly greater toxicity at higher doses.

Determining sensitivity of tumour cells to fractionation

Most tumours are rapidly growing and have high α/β values, making them sensitive to overall dose with less effect from fraction size. Some tumours, notably prostate cancer and melanoma, have low α/β values. This makes them more sensitive to **large** fraction sizes and resistant to small fraction sizes. In practice: high dose rate brachytherapy → delivers a small number of large doses to the vicinity of the prostate, has potential for increasing cure rates of prostate cancer.

Choosing fractionation schedules

Low α/β tissues typically suffer less toxicity at low doses compared with high α/β tissues. Most tumours also possess high α/β values. In areas where late toxicity requires high dose, such as in the skin or limbs, it is possible to shorten treatment times without significant late normal tissue toxicity. This becomes problematic in areas with organs sensitive to late effects; in these cases a more fractionated regime is recommended to exploit the cell kill between the tumour cells and late responding cells.

Clinical Use Of Dose Response Curves

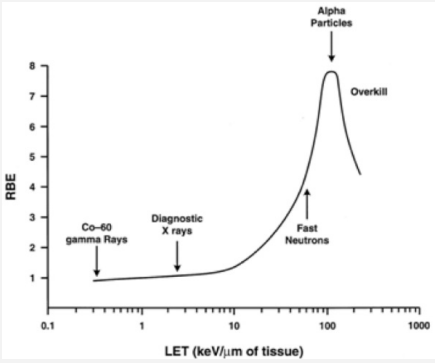
Clinical Applications (cont)

Dose response curves can be generated for tumour control or normal tissue complications. If compared, the ratio between the two curves at a particular dose is the therapeutic index. If the curves can be shifted (eg. by drugs, oxygenation etc) then the therapeutic index is altered, possibly providing a beneficial effect.

Chemotherapy and Dose Response Curves

Chemotherapy agents which sensitise cells to radiation will usually shift the tumour control and normal tissue complication curves to the left (a greater effect for a similar dose). If chemotherapy widens the gap between tumour control and normal tissue complications for a particular dose, then the therapeutic index will be improved and chemotherapy may be beneficial. This explains why, for some treatments, a reduced fraction size or dose is used when concurrent treatment is used instead of radiation alone.

RBE as a function of LET



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Not published yet.
Last updated 21st October, 2016.

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RBE as a function of LET

As LET increases, survival curves become steeper and the extrapolation number tends towards unity.

Another way to present these data is to plot the RBE as a function of LET.

As the LET increases, the RBE increases slowly at first and then more rapidly as the LET increases beyond 10 keV/µm, reaching a peak at about 100 keV/µm after which it falls again to lower values.

The shape of the survival curve for mammalian cells exposed to sparsely ionising radiation strongly suggests that more than one target in the cell must be inactivated before the cell will lose its reproductive integrity.

In order to understand the RBE/LET relationship, it is convenient to consider a cell as having two sensitive sites.

Low LET radiation produces ionising events that are well separated and in most cases only one event will be deposited per cell, which is insufficient to kill the cell. Cell kill is only possible when two separate particles pass through the cell.

At the peak of the graph, radiation is of optimum LET where the average distance between ionising events is just exactly matched to the average spacing between the sensitive sites in the cell.

This radiation is efficient at killing since no radiation is wasted.

As the LET is further increased, ionising events are clustered even closer together. The radiation becomes less efficient at killing cells because of the 'overkill effect'.

RBE as a function of LET (cont)

Many cells have three or more ionising events in them, when only two are necessary to kill; this leads to a waste of radiation

Therapeutic gain factor TGF

$$\text{TGF} = \frac{\text{RBE tumour}}{\text{RBE normal tissue}}$$

RBE for different cells and tissues

Even for a given total dose or dose per fraction, the RBE varies greatly according to the tissue or end point studied because of differences in the intrinsic radiosensitivity of various types of cells.

In general, cells characterised by an x-ray survival curve with a large shoulder, indicating that they can accumulate and repair a large amount of sublethal damage, will show a large RBE for neutrons.

Conversely, cells for which the x-ray survival curve has little if any shoulder will exhibit small neutron RBE values.

When considering the possibility of using neutrons for radiation therapy, we need to know the response of both tumour cells and normal cells.

For neutrons to be more effective than x-rays in a clinical case, the RBE for tumours would need to be larger than the RBE for the relevant dose-limiting tissue.

This is, the **therapeutic gain factor TGF**

Relative Biological Effectiveness (RBE)

$$\text{RBE} = \frac{\text{Dose of Standard Radiation}}{\text{Dose of Test Radiation}} \text{ for a given effect}$$

$$\text{RBE} = \frac{10}{1} = 10$$

For you (generally):

$$\text{RBE} = \frac{\text{Dose of 250 kVp x-rays required to produce effect X}}{\text{Dose of test radiation required to produce effect X}}$$

Relative Biological Effectiveness (RBE)

Equal doses of different types of ionising radiations do not produce equal biological effects and when comparing these effects, x-rays are routinely used as the standard.

Relative Biological Effectiveness (RBE) allows comparison of a test radiation with a standard radiation.

It is the ratio of dose between the radiations to give a certain biological effect.

For example, if 10 Gy of 60Co gamma rays kills 50% of the mice in a group, and 1 Gy of heavy ion radiotherapy kills the other group, the RBE would be 10/1=10

The **higher the RBE** for a type of radiation, the **more damaging** is the type of radiation, per unit of energy deposited in biological tissues.

RBE depends on a number of other factors:

The chosen biological effect: It may be that to kill 100% of the mice, a different ratio of doses is required.

Fractionation of each dose: Fractionation may split the survival curves of the mice, meaning that 20 Gy of gamma rays versus 1.5 Gy of heavy ions are required, giving a RBE of 13.3.

Changes in dose rate can also impact on the survival of cells. This can therefore alter the RBE.

In summary, it is found that the relative biological effectiveness depends on: 1. radiation quality (LET) 2. radiation dose 3. number of dose fractions 4. dose rate 5. biological system or end point.

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Low vs High LET

Low LET	High LET
< 10 keV/µm	> 10 keV/µm
Sparsely ionizing	Densely ionizing
Random interactions	Uniform Energy deposition
Penetrating	Superficial
External hazard	Internal hazard
Indirect	Direct
Single-strand break	Double-strand break
Mostly perfect repair	Highly error prone
Point mutation	Frameshift mutation
Sublethal	More likely lethal
Ex. X-ray, gamma	Charged particles

Linear Energy Transfer

When radiation is absorbed in biological material, the ionising events are localised along the tracks of the individual charged particles in a pattern that depends on the type of radiation involved as well as the density of the material.

The spatial distribution or density of these events can be classified as sparse, intermediate or dense.

Electrons (unit charge and small mass), set in motion by gamma photons or x-rays, are said to be sparsely ionising.

Neutrons give rise to recoil protons carrying unit charge but having a mass ~2000 times that of electrons. These have an intermediate ionising density.

Alpha-particles (double charge, mass 4 times proton) have a charge to mass ratio of 4000 times that of electrons and are said to be densely ionising.

Linear Energy Transfer (LET) accounts for all the energy liberated along the path of an ionising particle.

LET is the average amount of energy a particular radiation imparts to the local medium per unit length (ie. Energy per Length).

Linear Energy Transfer (cont)

It is defined as the ratio dE/dL where dE is the average energy (keV) deposited in the medium by a charged particle of specified energy in moving a distance dL (micrometers).

For radiotherapy, we are normally concerned about small amounts of energy over small distances, so the units we use are keV/µm.

The rate of loss of energy by ionising particles will be affected by the velocity of and the electronic charge on such a particle.

A relatively slow moving, highly charged particle will have a high LET because of their greater energy deposition along the track.

A faster moving particle and/or one with a lesser charge will have a much smaller LET.

In practice, most radiations are not mono-energetic but consist of a wide spectrum of energiesConsequently, the LET can only be an average quantity for such radiations.

Energy loss events are essentially randomly distributed along the track of the photon or charged particle.

For low LET radiations the energy deposition events along the track of the photon are sparse relative to the dimensions of biomolecules such as DNA with the result that photons may pass through such a molecule without depositing any energy.

For such radiations the amount of energy deposited in a region of the track similar in dimensions to biological molecules also various widely from a few eV up to 100s of eV.

Linear Energy Transfer (cont)

For high LET radiation the energy loss events are much more closely spaced and significant energy will be deposited along all parts of the track similar in dimension to biomolecules.

Radioresistance of cell types

High Radiosensitivity
Lymphoid organs, bone marrow, blood, testes, ovaries, intestines
Fairly High Radiosensitivity
Skin and other organs with epithelial cell lining (cornea, oral cavity, esophagus, rectum, bladder, vagina, uterine cervix, ureters)
Moderate Radiosensitivity
Optic lens, stomach, growing cartilage, fine vasculature, growing bone
Fairly Low Radiosensitivity
Mature cartilage or bones, salivary glands, respiratory organs, kidneys, liver, pancreas, thyroid, adrenal and pituitary glands
Low Radiosensitivity
Muscle, brain, spinal cord



Radiosensitivity

There is an intrinsic radiosensitivity or radioresistance in different cell types.

Radiosensitivity is the relative susceptibility of cells, tissues, organs or organisms to the harmful effect of ionising radiation.

In general, it has been found that cell radiosensitivity is directly proportional to the rate of cell division and inversely proportional to the degree of cell differentiation.

This means that actively dividing cells or those not fully mature are most at risk from radiation.

The most radio-sensitive cells are those which:
-have a high division rate
-have a high metabolic rate
-are of a non-specialised type
-are well nourished

Factors that Affect Cellular Radiosensitivity:

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Radiosensitivity (cont)

Conditional factors - physical or chemical factors that exist previous to and/or at irradiation:
Dose rate
LET
Fractionation
Presence of oxygen

Inherent factors - biologic factors characteristic of the cell:
Mitotic rate
Degree of differentiation
Cell cycle phase

Reoxygenation

Reoxygenation is the phenomenon by which tumours with hypoxic regions become oxic again during radiotherapy treatment.

Tumours under 1 mm in size are fully oxic, but tumours over this size develop regions of hypoxia.

Reoxygenation occurs through several proposed mechanisms:

1. Reopening of temporarily occluded blood vessels occurs in the minutes following radiation exposure

2. Reduced respiration of lethally damaged cells leads to increased oxygen supply to anoxic cells within minutes to hours of radiation

3. Death of cells due to mitotic catastrophe occurs within hours of radiotherapy. The resorption of dead cells leads to decreased distance from capillaries to tumour cells, improving their oxygen supply. This is the longest process, taking days.

Tumours contain a mixture of aerated and hypoxic cells. A dose of x-rays kills a greater proportion of aerated than hypoxic cells because they are more radiosensitive.

Immediately after irradiation, most cells in the tumour are hypoxic, but the pre-irradiation pattern tends to return because of reoxygenation.

Reoxygenation (cont)

There are numerous ways to overcome hypoxia, of which fractionation is the most commonly used in the modern setting.

Fractionation of dose kills oxygenated cells first, allowing the hypoxic population to migrate closer to the vascular network and become oxygenated.

The remaining fractionated dose then kills these previously hypoxic cells.

If the radiation is given in a series of fractions separated in time sufficient for reoxygenation to occur, the presence of hypoxic cells does not greatly influence the response of the tumour.

Repair of Radiation Damage

Radiation damage can be divided into three categories:

1. **Lethal damage**, which is irreversible, and leads to cell death;

2. **Potentially lethal damage**, which can be modified by post-irradiation environmental conditions; and

3. **Sublethal damage**, which under normal circumstances can be repaired in hours unless additional sublethal damage is added with which it can interact to form lethal damage.

Chronic Hypoxia

In a histological study of human bronchial carcinomas, it was found that larger tumours had many centres of dead cells, which were far from their source of nutrients and oxygen, and were surrounded by intact tumour cells that were close to blood vessels.

Chronic Hypoxia (cont)

As the tumours grew larger, the necrotic centres enlarged so that the thickness of the layer of viable cells remained almost constant.

Assuming a steadily decreasing oxygen concentration, cells lying between these two cell types would be at an oxygen tension high enough to survive but low enough to protect them from the effects of ionising radiation.

Consequently, these cells could provide the focus for the subsequent regrowth of the tumour following radiotherapy.

Chronic Hypoxia is due to the poor vasculature of tumours and the distance oxygen must travel to reach cells that are far from the capillaries.

These chronically hypoxic cells are also resistant to radiation.

Fractionated radiotherapy kills cells that lie close to the capillary more effectively. As these cells are removed, the chronically hypoxic cells are able to move closer to their nutrient source, and therefore become relatively oxic. Oxic cells can be killed.

Chronic and Acute Hypoxia of Tumours

Cellular hypoxia in tumours can be caused by two different mechanisms;

Chronic hypoxia, which is a consequence of the limited diffusion distance of oxygen.

Acute hypoxia, which results from the temporary closing of a blood vessel.

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Mechanism of the oxygen effect

It is believed that oxygen acts at the level of the free radicals.

When x-radiation is absorbed by tissue, fast charged particles are produced. These produce ion pairs. The ion pairs have a very short lifetime and produce free radicals that, because of their unpaired valance electrons, are highly reactive molecules.

In most cases, it is these free radicals that break chemical bonds and ultimately produce biological damage.

If oxygen is not present many of the ionised target molecules can repair themselves and recover the ability to function normally.

However, with oxygen present there is less chance that restoration of damaged molecules will occur.

Oxygen is said to 'fix' the radiation damage in the sense of making it permanent and the process is known as the **'oxygen fixation hypothesis'.**

The oxygen effect is large and important in the case of sparsely ionising radiations, such as x-rays, is absent for densely ionising radiations, such as α-particles, and has an intermediate value for moderately ionising radiations, such as 15-MeV neutrons.

This is because the actions of high-LET radiations are less susceptible to enhancement than that of low-LET radiations.

The oxygen effect is only important for the indirect component of radiation damage.

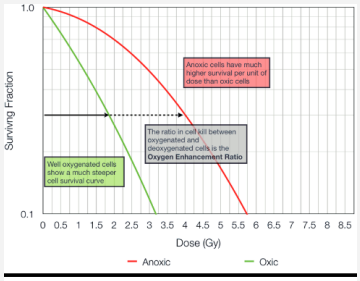
High-LET radiations are, in themselves, very effective at producing damage and very high LET radiations are so effective that the passage through a cell by one of them is lethal.

Mechanism of the oxygen effect (cont)

The oxygen effect has no known practical significance in diagnostic radiology or nuclear medicine. Radiations used are low-LET, but doses are so low that little cell killing occurs.

Its main significance is in radiotherapy. It is likely that most, if not all, cancers contain cells that are hypoxic and also some which probably are severely hypoxic.

The Oxygen Effect



$$\text{OER} = \frac{\text{Dose in anoxic conditions}}{\text{Dose in oxic conditions}}$$
for the same biological effect

The Oxygen Effect

Results from survival curves show that mammalian cells are much more radiosensitive to x-rays in the presence of oxygen (**oxic**) than they are in its absence (**anoxic**).

For some radiation types, there is a great difference in the biological effect seen in oxic versus anoxia conditions.

It is particularly important for radiation types that cause damage through indirect action (eg. photons, electrons).

This is because oxygen is required to 'fix', or make permanent, the damage caused by free radicals.

Without oxygen, the DNA radical that is created after reacting with the hydroxyl radical is simply repaired.

The Oxygen Effect (cont)

The ratio of hypoxic to aerated doses needed to achieve the same biological effect (for example, the same level of cell killing) is called the **oxygen enhancement ratio (OER).**

For low-LET radiation, it has a value close to 3 at high doses but may have a value of about 2 at doses below about 2 Gy (200 rads), which are typical of daily doses used in radiotherapy.

For photons and electrons, the OER approaches 3 for most cell types. This means that cell killing is three times more effective in oxic conditions versus anoxic conditions for indirectly acting radiation.

Radiation types that rely more on **direct action** (eg. protons, alpha particles, heavy ions) show minimal changes in the presence or absence of oxygen.

This is because oxygen is not required to 'fix' the damage caused by these radiations, as they interact directly with the DNA molecule to cause damage.

The oxygen effect is seen in cell survival curves as a shift in the steepness of the curve.

Dose-Rate Effect

Dose rate is one of the principal factors that determine the biological consequences of a given absorbed dose from low-LET radiation.

As the dose rate is lowered and the exposure time extended, the biological effect is generally reduced.

The magnitude of the dose-rate effect from the repair of sublethal damage varies enormously between different types of cells.

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Dose-Rate Effect (cont)

Cells such as HeLa, which have a survival curve with a small initial shoulder, show only a modest dose-rate effect.

Chinese hamster cells have a broad shoulder to their survival curve and show a large dose-rate effect.

Three main biologic processes are involved:

1. **Repair of sublethal damage** occurs when radiation is delivered at a low dose rate, and the treatment time is extended to a point where it is comparable to the repair half-time. As the dose rate is reduced, more sublethal damage is repaired because the radiation injury is spread over a longer period. The cell survival curves become progressively less steep, and at the same time the extrapolation number approaches unity.

2. **Cell proliferation** occurs during protracted radiation exposure if the dose rate is low enough or the cell cycle time is short enough.

3. **Reassortment and accumulation of cells** throughout the cell cycle occur with a low dose rate in which proliferation is decreased because cells are arrested and accumulate in G2. This phase of the cycle is relatively radiosensitive. As a result, cell killing may be greater for a lower dose rate. This effect occurs over a narrow dose-rate range and is known as the inverse dose-rate effect.

Repopulation

As cellular damage and cell death occur during the course of the treatment, the tissue may respond with an increased rate of cell proliferation.

Repopulation (cont)

The effect of this cell proliferation during treatment, known as repopulation (regeneration), will be to increase the number of cells during the course of the treatment and **reduce the overall response to irradiation.**

This effect is most important in early-responding normal tissues (e.g., skin, gastrointestinal tract) or in tumours whose stem cells are capable of rapid proliferation.

It will be of little consequence in late-responding, slowly proliferating tissues (e.g., kidney), which do not suffer much early cell death and hence do not produce an early proliferative response to the radiation treatment.

Important factor influencing local tumour control in patients with head and neck or cervical cancer.

Local control is reduced by approximately 0.5 percent for each day that overall treatment time is prolonged.

Repopulation provides the biological rationale for accelerating fractionated radiation therapy.

Repopulation is likely to be more important toward the end of a course of treatment, when sufficient damage has accumulated (and cell death occurred) to induce a regenerative response - for tumours as well as for normal tissues.

Reassortment/Redistribution

Variation in the radiosensitivity of cells in different phases of the cell cycle results in the cells in the more resistant phases being more likely to survive a dose of radiation.

Two effects can make the cell population **more sensitive** to a subsequent dose of radiation:

Reassortment/Redistribution (cont)

1. Some of the cells will be blocked in the G2 phase of the cycle, which is usually a sensitive phase.

2. Some of the surviving cells will redistribute into more sensitive parts of the cell cycle.

Both effects will tend to make the whole population more sensitive to fractionated treatment as compared with a single dose.

When radiotherapy is given to a population of cells, they may be in different parts of the cell cycle.

Cells in S-phase are typically radioresistant, whereas those in late G2 and M phase are relatively sensitive.

A small dose of radiation delivered over a short time period (external beam or high dose brachytherapy) will kill a lot of the sensitive cells and less of the resistant cells.

Over time, the surviving cells will continue to cycle. If a second dose of radiation is delivered some time later, some of these cells will have left the resistant phase and be in a more sensitive phase, allowing them to be killed more easily.

As reassortment inevitably involves cell proliferation, the survival will also be influenced by repopulation, which reduces the effect of reassortment.

Both reassortment and repopulation are important primarily in proliferating cell populations.

In many normal tissues (and probably in some tumours), stem cells can be in a resting phase (G0) but can be recruited into the cell cycle to repopulate the tissue.

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Not published yet.
Last updated 21st October, 2016.

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Reassortment/Redistribution (cont)

There is some evidence that cells in cycle are slightly more sensitive to radiation than G0 cells, possibly because G0 cells may repair more potentially lethal damage.

Recruitment of resting cells into the proliferative cycle during the course of fractionated treatment, therefore, may tend to increase the sensitivity of the whole population.

Neither recruitment nor reassortment would be expected to have much influence on late responses that occur predominantly as a result of injury to tissues in which the rate of proliferation is low.

Repair

One of the primary reasons to fractionate radiotherapy.

By splitting radiation dose into small parts, cells are allowed to repair sublethal damage.

The amount of damage that is repaired depends on the ability of the cell to recognise the damage and activate a) **repair pathways** and b) **cell cycle arrest.**

Malignant cells have often suppressed these pathways, often through mutation or inhibition of TP53, preventing them from undergoing efficient repair.

Normal tissue cells with intact repair pathways are able to repair the sublethal damage by the time the next fraction is delivered.

The shoulder on a survival curve after single radiation doses is indicative of the capacity of the cells to accumulate and repair radiation damage.

Repair (cont)

If multiple doses are given with sufficient time between the fractions for repair to occur (4 to 24 hrs depending on the cells or tissue involved) the effective survival curves is straight on a semi-logarithmic plot and has a shallower slope than the curve for big single doses (ie. Repair is responsible for shoulder of survival curve).

The effective slope depends on the size of the individual dose fractions, becoming shallower as the fraction size is reduced. This effect is also seen for irradiation of different tissues.

The single dose survival curve for most cells has a finite initial slope apparently due to a (single-hit) non-repairable damage component, so there is a limit below which further reduction of the fraction size will no longer reduce the effective slope of the survival curve.

At this limit, essentially all the repairable damage is being repaired between each fraction so that the cell killing is due almost entirely to non-repairable events.

The fraction size at which this limit is reached is different for different cell populations depending on their repair capacity.

When the size of the individual dose fractions is such that the survival is represented by the shoulder region of the survival curve, as for most dose fractions used clinically, then repair will be maximal when equal-sized dose fractions are given.

Split-Dose Experiments

Recovery from sublethal damage is demonstrated by split-dose experiments.

Cells are exposed to sufficient radiation so that any survivors will have accumulated the maximum amount of sublethal damage.

After a time interval, the survivors are irradiated again. In the absence of any recovery, the proportion of irradiated cells expected to survive the two radiation exposures should be the same as would survive a single radiation exposure equal to the sum of the two doses.

In experiments, however, the observed proportion of survivors can be greater than this. In the time between the two exposures, cells that survive the first exposure are thought to recover from damage done during that exposure.

The pattern of repair is a combination of three processes occurring simultaneously:

1. **Repair**: First there is the prompt repair of sublethal radiation damage.

2. **Reassortment/Redistribution**: Second there is progression of cells through the cell cycle during the interval between the split doses.

3. **Repopulation**: Third, there is an increase of surviving fraction due to cell division when the interval between the split doses exceeds the cell cycle.

The dramatic dip in the split-dose curve at six hours, caused by reassortment, and the increase in survival by 12 hours, because of repopulation, is seen only for rapidly growing cells.

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Not published yet.
Last updated 21st October, 2016.

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Split-Dose Experiments (cont)

The phenomenon of repair is one of the important factors in the sparing effect on normal tissues by the multi-fraction dosage regimens that are commonly used in radiotherapy, even though sublethal damage repair occurs in both tumours and normal tissues.

Sublethal Damage

Thought to be responsible for shoulders on survival curves.

The existence of this form of damage is inferred from the shape of the survival curves, but so far it has not been demonstrated directly.

Survival curves are a graphic representation of the relationship between the fraction of cells surviving and those being killed by given radiation doses. Survival curves, therefore, are a record of the production of lethal damage.

Sublethal damage is presumed to occur because of the steep slope in the dose range beyond the shoulder.

The change in slope shows increased vulnerability to radiation at higher doses, suggesting an accumulation of sublethal injuries has occurred in the low- dose range and is reaching lethal levels in the high-dose range.

The sublethal injuries themselves are not detected; the only time anything is noted is when a cell is lethally injured and dies.

Potentially Lethal Damage (PLD)

Under normal circumstances PLD is lethal, but under others is not.

If we irradiate two identical cell populations with single doses of low-LET radiation under identical conditions, the probability of survival will differ according to the post-irradiation conditions.

PLD is repaired and the survival fraction is increased if post- irradiation conditions are sub-optimal for growth, so that cells do not have to attempt mitosis while their chromosomes are damaged.

If mitosis is delayed, DNA damage can be repaired.

Therefore, there is a form of injury which can cause death in cells that are actively replicating, but which is not lethal in cells that are resting.

In clinical radiation therapy, the importance of PLD repair is still not proved. However, it may be responsible for the radioresistance exhibited by some tumours, that is, these tumours can repair PLD efficiently, but this is still a matter of debate.

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