Name: _____   Date: _____

In this exam sheet, there are 18 questions.
Each answer yields up to 2 points according to its correctness and completeness.

1. What is the superoxide anion? Why is it important in radiobiology?

2. When ionizing particles pass through water, they produce many radiolytic species: **a.** list at least 3 types of radiolytic species; **b.** are these products equally damaging to cells?

3. What is the difference between somatic cells and germ cells, and how is this important in radiation biology? (explain)

4. Explain what stroma, parenchima and epithelium are.

5. What are the codons and how many different codons exist?

6. What are the introns? And what are the exons?

7. What is a gene? How is it used in cells? (explain)

8. Explain how the degree of hypoxia of the tumor microenvironment can affect radiotherapy.

9. What is clonogenic death?

10. What is the Poisson model of survival of irradiated cells? What is the mathematical expression for the surviving fraction in the Poisson model?

11. Why is the Poisson model inadequate to describe the observed surviving fraction? What is the empirical model that is most commonly used to describe the surviving fraction for doses no larger than about 6 Gy?

12. Describe the multitarget model, derive its mathematical expression, and compare it to the Poisson model of the surviving fraction.

13. The following image – taken from Barendsen, Proc. Conf. "Microdosimetry", Ispra 1967 – illustrates an important feature of the survival curve. Explain the meaning of the plots
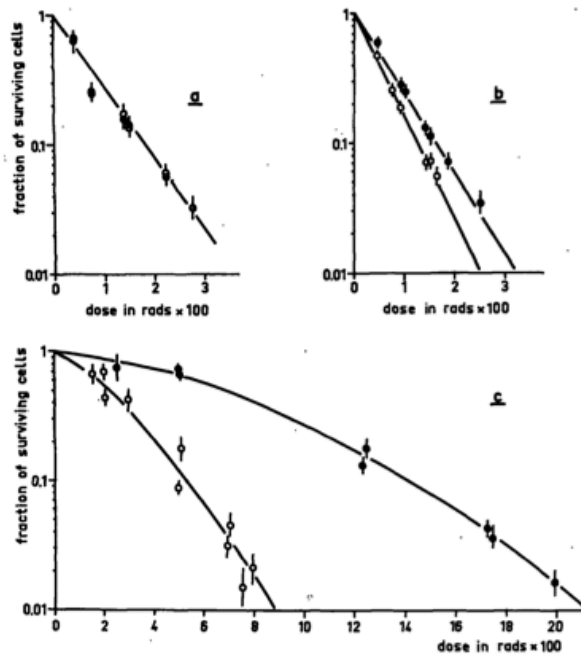

Figure 2. Dose-survival curves for cultured cells of human origin in equilibrium with air and nitrogen respectively: open symbols, air; filled symbols, nitrogen. (a) 2.5 MeV α-particles, $LET_\infty = 166$ keV/μ, OER = 1.0 + 0.1. (b) 4.0 MeV α-particles, $LET_\infty = 110$ keV/μ, OER = 1.3 ± 0.1. (c) 14.9 MeV deuterons, $LET_\infty = 5.6$ keV/μ, OER = 2.6 ± 0.3.

14. What is the mathematical expression of the TCP in the context of the multitarget model?

15. The U-251MG cell line (one of the cell lines of the brain tumor *glioblastoma multiforme*) has the following LQ parameters: $\alpha = 0.36$ Gy^{-1} and $\beta = 0.06$ Gy^{-2}. When we irradiate these cells in a fractionated treatment with a series of 2 Gy doses, what is the effective D_0?
(Hint: the effective D_0 is defined in the Poisson model description of the surviving fraction: $S(D) = e^{-D/D_0}$)

16. Explain the concept of Equivalent Uniform Dose.

17. What is a dose-volume histogram? Explain how it is read.

18. What is the expression for the biologically effective dose (BED) and how is it corrected for cell proliferation?

Answers

1. The superoxide anion is the ion O_2^-, as in the figure.

Human cells use the superoxide anion to kill bacteria. The enzymes of the complex NADPH oxidase (NOX) produce superoxide. The superoxide anion is toxic to human cells, and this requires mechanisms to get rid of it, like the enzyme superoxide dismutase.
The superoxide anion is produced by ionizing radiation and it is one of the ROS that help killing tumor cells.

2. The radiolysis of water is the process by which water molecules are broken into ions by the action of ionizing particles. The resulting ions can combine with neighboring water molecules or other ions to form several types of radiochemical species. Common radiolytic species are O_2^-, H_2O_2, OH^-, OH, H_3O^+, e_{acq}^-. These species vary in their damage potential.

3. Germ cells are either a sperm or an egg, all other human cells are called somatic cells. Radiation-induced mutations in germ cells can propagate to the progeny. Radiation-induced mutations in somatic cells do not propagate to the progeny, but can produce radiation-related pathologies and lead to cancer.

4. The stroma is that part of tissue or organ that has connective and structural role (like connective tissue, blood vessels, nerves, etc.). The parenchima is that part of tissue that performs the function of the tissue or organ. Finally, the epithelium is a tissue that lines cavities and surfaces of blood vessels and organs.

5. A codon is a triplet of nucleotides that encodes an aminoacid or an instruction that corresponds to the start or stop of the genetic sequence that encodes a whole gene. Since there are 4 types of nucleotides, there are 4^3 = 64 different codons.

6. The introns are the noncoding sections of DNA. The exons are the coding sections of DNA.

7. A gene is a unit of heredity that occupies a fixed position on a chromosome. When a gene is *expressed* it is copied onto messenger RNA (mRNA). When the mRNA is detected by a ribosome, it is translated into a protein.

8. Radiation kills cells more effectively when oxygen is copious: this is the Oxygen Effect. A hypoxic tumor microenvironment means that radiation is less effective in killing tumor cells.

9. Clonogenic death occurs when a cell is unable to form clones, i.e., to proliferate.

10. In the Poisson model, a cell dies if a single sensitive target is hit; in this model, the probability of NOT being hit is $S(D) = e^{-D/D_0}$, and this is also the expression of the survival probability in the Poisson model.

11. The Poisson model fails describe the behavior of the survival fraction for low doses. The most common description is the linear-quadratic model, which is used in the range between 1 and 6 Gy.

12. In the Poisson model, a cell dies if a single sensitive target is hit; in this model, the probability of NOT being hit is $S(D) = e^{-D/D_0}$. In the multitarget model we assume that a cell dies only when multiple targets are all hit. So, if the Poisson probability of not hitting a given target is e^{-D/D_0}, then the probability of hitting the same target *at least once* is $1 - e^{-D/D_0}$, and therefore the probability of hitting *all* of the n targets at least once is $(1 - e^{-D/D_0})^n$, and finally, the probability of NOT hitting all of them at least once is

$$S(D) = 1 - (1 - e^{-D/D_0})^n$$

13. The figure shows the OER for different particles and different values of LET. The oxygen effect is quite apparent for low LET (panel c). At higher LET (panel b) the effect is much less apparent, and at higher still LET (panel a) it disappears completely.

14. The TCP is the probability of killing all the cells in a tumor. If the tumor has N cells then the average number of surviving cells is $NS(D)$, and the probability that no cell survives is $e^{-NS(D)}$. When we use the multitarget model, we find

$$TCP = e^{-NS(D)} = e^{-N(1-(1-e^{-D/D_0})^n)}$$

15. The surviving fraction in the LQ model is described by the expression

$$S(D) = e^{-(\alpha D + \beta D^2)}$$

In the present case $\alpha D = 0.72$; $\beta D^2 = 0.24$, and therefore $\ln S(2\text{ Gy}) = -0.96 = -\frac{2\text{ Gy}}{D_0}$. Thus, $D_0 \approx 2.08$ Gy.

16. For any dose distribution, the corresponding Equivalent Uniform Dose (EUD) is the dose in Gy, which, when distributed uniformly across the target volume, causes the survival of the same number of clonogens. Therefore, two different nonuniform target dose distributions are equivalent, i.e., they have the same EUD, if the corresponding expected number of surviving clonogens are equal.

17. Dose Volume Histograms (DVH) are empirical cumulative distributions of dose that are often used in radiotherapy. The horizontal scale represents dose, and the vertical scale represents a fraction of a population of cells. DVH's are read off so that for a given dose, the corresponding number on the vertical scale represents the fraction of cells that receives *at least* that dose.

18. The survival probability with n doses D is $[S(D)]^n$, and the corresponding biological effect is

$$E = -\ln[S(D)]^n = -n\ln S(D)$$
$$= n(\alpha D + \beta D^2)$$
$$= \alpha(nD)\left(1 + \frac{D}{\alpha/\beta}\right)$$

The biologically effective dose is defined as follows

$$\text{BED} = \frac{E}{\alpha} = (nD)\left(1 + \frac{D}{\alpha/\beta}\right)$$

After a "kickoff time" T_k, tumor cells start proliferating again, therefore the tumor population after treatment changes by the total factor

$$N(T)/N_0 = [S(D)]^n 2^{(T-T_k)/T_p}$$

where T_p is the tumor cells' duplication time. Taking logarithms, one finds

$$n\ln[S(D)] + \frac{T-T_k}{T_p/\ln 2} = -\alpha nD\left(1 + \frac{D}{\alpha/\beta}\right) + \frac{T-T_k}{T_p/\ln 2}$$

and finally

$$\text{BED}(D,n,T) = (nD)\left(1 + \frac{D}{\alpha/\beta}\right) - \frac{T-T_k}{\alpha T_p/\ln 2}$$
$$= \text{BED}(D,n) - \frac{T-T_k}{\alpha T_p/\ln 2}$$