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 radiolysis of water?

2. Using the table below, find **a.** how many of H_3O^+ ions are produced, on average, when 10^5 electrons – each with 10 keV kinetic energy – stop in water, and **b.** how many e^-_{aq} ions are produced by in the same process.

Table 13.3 *G* Values (Number per 100 eV) for Various Species in Water at 0.28 μs for Electrons at Several Energies

	Electron Energy (eV)							
Species	**100**	**200**	**500**	**750**	**1000**	**5000**	**10,000**	**20,000**
OH	1.17	0.72	0.46	0.39	0.39	0.74	1.05	1.10
H_3O^+	4.97	5.01	4.88	4.97	4.86	5.03	5.19	5.13
e^-_{aq}	1.87	1.44	0.82	0.71	0.62	0.89	1.18	1.13
H	2.52	2.12	1.96	1.91	1.96	1.93	1.90	1.99
H_2	0.74	0.86	0.99	0.95	0.93	0.84	0.81	0.80
H_2O_2	1.84	2.04	2.04	2.00	1.97	1.86	1.81	1.80
Fe^{3+}	17.9	15.5	12.7	12.3	12.6	12.9	13.9	14.1

3. What is the approximate volume of a human cell? How many cells are there in 1 cm^3?

4. Explain what parenchima, stroma and epithelium are.

5. What is the LD_{50} radiation dose for a human being? And what is the LD_{50} radiation dose for an extremophile like the D. radiodurans?

6. What is a stem cell? (explain)

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

8. What is superoxide dismutase? Why is it important?

9. What is the difference between necrosis and clonogenic death?

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

11. What is range of validity of the linear-quadratic model? Is it correct to utilize the linear-quadratic model in a fractionated radiotherapy with a total dose of 100 Gy? (explain)

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.

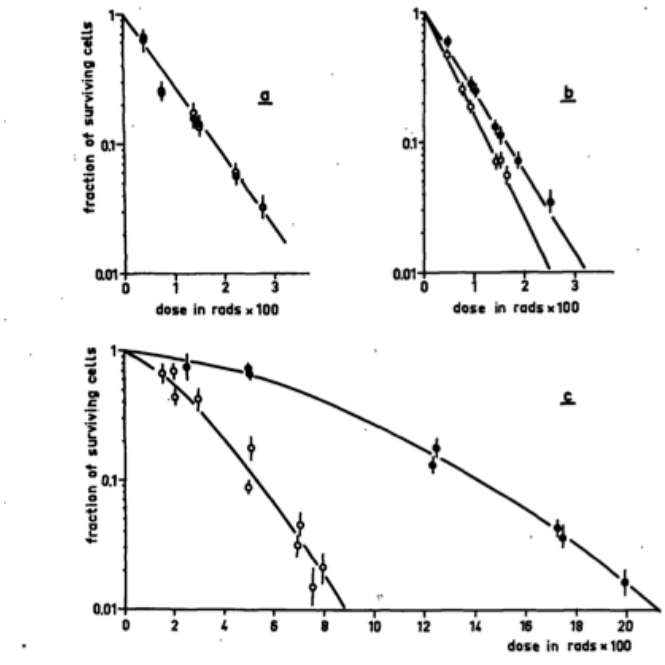


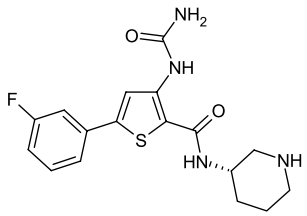
Figure 2. Dose-survival curves for cultured cells of human origin in equilibrium with air and nitrogen respectively: open symbols, air; filled symbols, nitrogen. (a) 2.5 MeV α-particles, LET_∞ = 166 keV/μ, OER = 1.0 + 0.1. (b) 4.0 MeV α-particles, LET_∞ = 110 keV/μ, OER = 1.3 ± 0.1. (c) 14.9 MeV deuterons, LET_∞ = 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. What is the expression for the biologically effective dose (BED) and how is it corrected for cell proliferation?

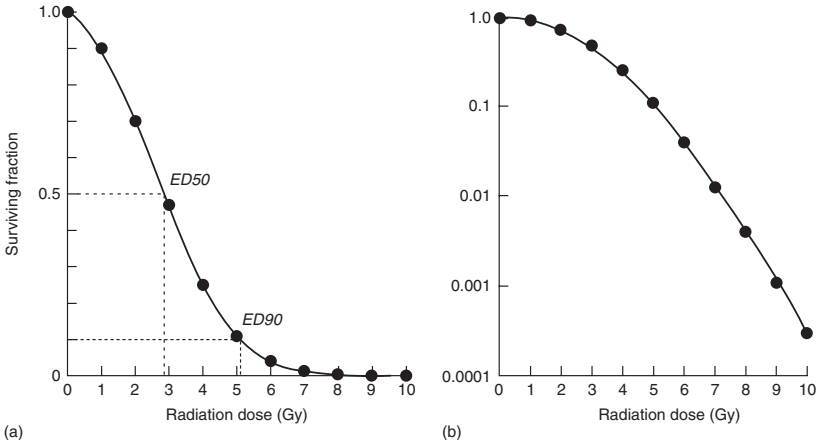
17. AZD7762 is a novel drug that is administered in combination with DNA-damaging agents, to enhance the efficacy of both conventional chemotherapy and radiotherapy and increase patient response rates in a variety of settings.



AZD7762

It works by abrogating the S and G2 checkpoints. How does this explain its radiosensitizing activity?

18. A trivial question: consider the following figures, which represent survival curves. How do these survival curves differ? Motivate your answer.



Answers

1. 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.

2. $5.19 \cdot 10^7$ H_3O^+ ions; $1.18 \cdot 10^7$ OH^- ions.

3. We can approximate human cells as spheres with radius ~ 10 μm. Then, their volume is about 4×10^3 μm^3 = 4×10^{-15} m^3. This means that in 1 cm^3 = 10^{-6} m^3, we can fit about 2.5×10^8 cells.

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

5. The LD_{50} radiation dose for a human is about 5 Gy. The LD_{50} radiation dose for D. radiodurans is about 5000 Gy.

6. Stem cells are undifferentiated cells that can differentiate into specialized cells and can divide (through mitosis) to produce more stem cells. In mammals, there are two broad types of stem cells: embryonic stem cells, and adult stem cells, which are found in various tissues.

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

8. Superoxide dismutase is an enzyme that converts the superoxide anion (O_2^-) into either ordinary molecular oxygen or hydrogen peroxide (H_2O_2). This is an important defense mechanism against DNA damage, because O_2^- is an extremely aggressive ROS.

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

10. 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 because of the greatly reduced Oxygen Effect.

11. The linear-quadratic model is valid for an absorbed dose lower than about 6 Gy. Even though fractionated therapy may lead to exposures of more than 100 Gy, the linear-quadratic model is applicable because the total radiation in each fraction is less than the 6 Gy limit for the validity of the model.

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

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

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

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

and finally

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

17. When DNA is damaged a proliferating cell stops at checkpoints to repair DNA and the cell cycle restarts only when the repair is complete. By abrogating checkpoints in combination with DNA-damaging agents, it is thus possible to kill proliferating cells.

18. The curves represent the same data, but the curve on the right has a logarithmic vertical scale.