DOSE-RATE AND FRACTIONATION EFFECTS
OF IONIZATION RADIATION*

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In today's seminar I propose to compare a number of theories and models that have been considered to explain dose-rate and fractionation effects. The purpose is to acquaint you with these theories and the ideas that motivated their development.

The Phenomena

First, let us look at examples of the dose-rate and fractionation effects that I am talking about so that you may understand what I am including and what I am leaving out.

Dose-Rate Effect: Figure 1 shows a typical family of survival curves for synchronized cells for different dose rates. The dose rate is different for each curve but the same all along a given curve.

The curves for all of the dose rates lie between two limiting curves. As the rates become lower, the curves crowd closer and closer to a low-rate limit. On this conventional plot, which shows the logarithm of the fraction of the cell population that survives a given dose versus that dose, the low-rate limit is a straight line. As the rate becomes high, the curves crowd toward a high-rate limit which is a curved line.

Split-Dose Effect: Figure 2 shows a typical family of survival curves for synchronized cells for doses delivered in two fractions. The first dose was sufficient to reduce the survival to 10%. The numbers on the curves are the times between the doses measured in units of the mean recovery time, see below. Thus the curve marked "0" is just the ordinary one-dose survival, which is shown dashed between 100% and 10%.

When the time between the two doses is small, the survival curve is close to that for a single dose. As the time increases, the survival increases; however it approaches the limit shown by the dashed curve. This limiting curve is the dashed curve shown between 100% and 10% translated downward and to the right so the 100% point has been moved to coincide with the 10% point. This implies that for long inter-fraction times the remaining population reacts to the radiation as though it had not been irradiated before. Mathematically the limiting curve is given by $S = S_1 S_2$, where S_1 and S_2 are the single-dose survivals to the two doses given.

Effect of Mitotic Movement Excluded: Those of you who are familiar with split-dose data know that usually the curves, unlike those in Fig. 2, cross one another and are otherwise generally more complicated. The complications have been attributed to movement of the cells in their mitotic cycle to phases of different radiosensitivity in the period between the doses. If the

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Fig. 1

Fig. 2

cells move slowly or there is no change in sensitivity, the complications do not appear. We will assume that they are absent. We will also assume they are absent in the dose-rate effect.

The Basic Theory

We will shortly examine a number of theories or models that have been advanced to explain dose-rate and split-dose effects and that are all based on a common idea. This idea is that an individual charged particle that passes through a cell may produce a kind of damage that is not by itself fatal; it must combine with a complementary form of damage produced by another charged particle before it is fatal. Also, and equally important, the initial damage must be able to disappear, or to be modified into an innocuous form, in the interval before the complementary damage is formed by a later particle; we will generally refer to this as "recovery".

These two assumptions imply that the chance of a cell surviving depends on the average time between passages of charged particles through it. This average time changes when we change the dose rate: the average time increases as the dose rate decreases. As the time between passages increases, there is a greater chance for recovery to occur; thus the chance of the cell surviving increases -- that is what Fig. 1 shows.

Also, the average time between passages of particles in the first dose of a split dose and passages of those in the second dose is increased when the time between the two doses is increased. As before, this causes an increase in survival; this is what Fig. 2 shows.

If one decreases the time between passages (increases the dose rate or decreases the inter-fraction time), finally further decreases have no effect -- see the figures. There is finally so little time between charged particles that recovery has no chance to occur. With no recovery the maximum possible lethal effect will be produced, i.e. the survival will be a minimum at high dose rates and small inter-fraction times.

If one increases the time between passages (decreases the dose rate or increases the inter-fraction times), finally further increases have no effect -- see the figures. There is finally so much time between the charged particles that complete recovery can occur; once recovery is complete, no fatalities can occur. However, even though the recovery is complete, some cells are still killed. This is because, in addition to the "two-event" phenomena that we have here been talking about, there are "one-event" phenomena, types of fatal damage that occur as the result of the passage of a single charged particle. Since one-event killing is produced by single particles, it does not depend on the time between particles and, hence, is uninfluenced by dose-rate or fractionation; it depends only on the number of particles, i.e. on the absorbed dose. The one-event effect is superimposed on the two-event effect and accounts for the lethality that occurs when complete recovery of the two-event damage has taken place.

[Notice that "recovery" can occur for one-event damage as well as for two-event damage, i.e. the damage can be produced but may disappear or be modified before it is fatally expressed in the cell. This kind of recovery is of no interest to us at present, because it does not manifest itself in dose-rate or split-dose effects. To so manifest itself, a second

charged particle would have to be necessary -- contrary to the definition of one-event damage.]

[Similarly, a second kind of recovery could occur in the two-event damage: recovery of the otherwise fatal complex of damage resulting from the two charged particles. Again this is of no present interest because, since no subsequent charged particles are involved, it will not cause a dose-rate or split-dose effect.]

Recovery Theories

The preceding development of the basic theory gives a qualitative explanation of dose-rate and split-dose effects. We also want to explain them quantitatively. By this I mean, for now, that, if one were given one survival curve (so he could determine any unknown parameters in a theory), he could calculate the survival curve for any other dose-rate or for a split-dose experiment.

To do this requires extending the two assumptions we have already made. One has to know something about the relationship between the damage produced by the two charged particles and something about the rate of recovery of the damage due to the first one.

There is not time to examine all of the theories that have been advanced; I have chosen a few that illustrate important points.

Rajewsky and Danzer: Rajewsky and Danzer (1934) and later Lea (1938), introduced a very simple model. They said: suppose that the damage produced by the first charged particle lasts for exactly a time t and then disappears. Further, suppose that, if the second charged particle arrives within this time t , the result is certain to be lethal; if it comes later there is no result other than production of damage of the first kind that in turn will last for a time t .

We will examine the quantitative predictions of the theories below. For now, notice that we have here the two assumptions we spoke of above. The relationship between the damage by the two particles is that lethality is certain to occur if the two happen within the time t . It is the "is certain" that makes the model mathematically tractable. However, it is also the reason for the unrealistic results the model gives, see below. It is also unrealistic physically. Particles of low-LET radiations do not always produce damage when they go through a cell (or, better, through a critical region of the cell); therefore, they cannot with certainty produce an interaction with previous damage. Neither can the initial damage be produced by every particle.

The other assumption, the rate of recovery, is the sudden switch from 100% damage to 0% at the time t . This is a physical possibility. It could be the mathematical approximation to a recovery process that requires a large number of short steps; such a process would give an S-shaped recovery curve which, if it were narrow enough, could be approximated by a step function. The assumption is unique, however, among those that will be discussed today. All of the other theories assume that the recovery is gradual -- that the rate of decrease in the damage is proportional to the remaining damage, what is referred to as exponential recovery.

Two-State Model: In 1931 Swann and del Rosario introduced the first mathematical theory of radiobiological effects that I know of. Several other authors have further developed their theory, particularly Kellner and Hug (1963) and Dienes (1966). The main idea is that during an irradiation cells can be thought of as being in one of two classes (or states): damaged and undamaged (also, if you wish, a third class, dead or fatally injured). This is diagrammed:

The arrows going from left to right indicate what changes in class are possible when a charged particle goes through the cell. The long arrow from "undamaged" to "dead" corresponds to the one-event killing mentioned above. The two steps from "undamaged" to "damaged" to "dead" are the two-event killing that we are interested in. The reverse arrow from "damaged" to "undamaged" indicates the recovery process.

For each arrow there is a rate at which the cells make the indicated transition. For all the transitions it is assumed that the rate is proportional to the number of cells in the state where the arrow starts. (For the recovery process, this means exponential recovery as mentioned above.) The constants of proportionality are called "transition probabilities". They do represent probabilities, because, unlike Rajewsky and Danzer, it is not assumed that any particular transition is certain on the passage of a charged particle -- is only assumed that the average overall rate is fixed. The transition probabilities give time rates; therefore, those for production of damage are proportional to the dose rate of the radiation -- this is how dose-rate and split-dose effects arise.

[Most of you are familiar with target theory, where it is assumed that a cell contains N targets each of which must be hit M times by charged particles to kill the cell. The target theory obviously says nothing about dose-rate or split-dose effects. It is of interest, however, that -- with certain choices of the transition probabilities -- the two-state model leads to either the one-target, two-hit or the two-target, one-hit equations as the equations for the limiting survival curve at high dose rates. Also, the model can be extended to more than two states (by admitting states for different kinds of damage), and these extended models can lead to N -target, M -hit equations for the high-rate limit. On the other hand, these state models can lead to non-target-theory equations for the high-rate limit too.]

Roesch: The two-state model obviously does not entertain the possibility of there being different "amounts" of damage. Once a cell has been damaged it can be struck again by several more charged particles without being killed (because the transitions are probabilistic) and without any increase in the chance of being killed (the latter is what I mean by increase in the "amount" of damage). This is not a damning criticism; the model applies to phenomena in which a unique site has to be damaged to produce death.

Roesch (1967) introduced a model aimed at allowing for amounts of damage. He assumed that as long as the cell was not fatally injured it could go on accumulating damage of the first type from each particle that struck it. This damage would recover exponentially starting from the time it was produced. Any particle after the first can complement the damage from any preceding

particle. Thus one has to consider the possibility that death may result from any pair of charged particles. It presents a difficult, but manageable, mathematical problem.

Lajtha and Oliver: The last theory we will consider today assumes exponential recovery, as the two previous ones have, but relates the damage produced by different charged particles in a quite different way. Lajtha and Oliver's theory is that the decrease in survival produced by an increment in the dose depends only on the amount of the first type of damage remaining when the increment is delivered.

To find out how it depends on the damage that remains, they use the limiting survival curve for high dose rates. As we remarked above, the characteristic of this limiting curve is that none of the damage had a chance to recover: at every point on the curve, all of the primary damage produced contributes to the lethality. Thus it contains the information Lajtha and Oliver want -- they can assume that the amount of damage present is proportional to the dose, D , and can read from the curve the decrement, ΔS , in the survival for the increment, ΔD , in dose. At lower dose rates the damage has a chance to recover, so the amount of damage is proportional to $D(1 - e^{-t/\tau})$, where t is the irradiation time and τ is a constant called the mean recovery time. One then reads the ΔS from the high-rate curve at the dose $D(1 - e^{-t/\tau})$ rather than at D , but he plots it at the dose D to get the survival curve for the lower dose rate.

One can, of course, apply this procedure to any high-rate survival curve that he wishes. Each different curve will give him a different model based on the theory. It is of interest to compare the Lajtha-Oliver theory with those above by using their high-rate limits as model-generating curves.

If their theory is applied to the high-rate limit of the two-state model, the resulting survival curves for lower dose rates are not the same as those given by the two-state model. Specific numerical examples will be given below in Fig. 3. The numerical differences are not very large. The important thing is that the Lajtha-Oliver and the two-state models are conceptually different. The reason for the difference is that the Lajtha-Oliver theory presumes differences in amount of damage while the two-state model does not.

If their theory is applied to the high-rate limit of Roesch's model, the resulting survival curves for lower dose rates are identical to those Roesch found. One would like to know if other theories that allow for accumulation of damage would give this kind of agreement when used with the Lajtha-Oliver theory, but no one knows as yet.

Theoretical Dose-Rate Effect

Each of the models described above gives a family of dose-rate curves similar to that of Fig. 1. It is difficult to make a meaningful comparison of such families by plotting them on top of one another. Therefore, what has been done in Fig. 3 is to take one point from each curve of a family, the survival at a given dose, and plot it versus the dose rate. Families were chosen that had the same high-rate and low-rate survivals at that dose. This gives us a clearer picture of how things change with dose rate.

Fig. 3

Fig. 4

The first impression one gets is that there is not very much difference between the different curves except in the case of the Rajewsky-Danzer model. The differences can be reduced still further by shifting the curves to the left or right; this can be done by adjusting the recovery rate.

The lack of any clear differences means that identification of the applicable model by dose-rate tests is unlikely. This should not be discouraging news, however, because that is not usually what one tries to do. It has been known for decades that one cannot identify the applicable model by fitting curves to survival data; it is generally assumed that the same is true of other kinds of curves. What one is usually trying to do in fitting curves to data is to determine the parameters of a model. Justification of the use of the model may hinge on whether those values are reasonable or not, but it is more likely to come some other way.

The Rajewsky-Danzer model is clearly different from the others. The rate of change with dose rate is smaller than the others and probably smaller than in any experimental observations. The transition from change with dose rate to no change occurs at high rates (just above 1000 rad/min) with physically unlikely abruptness.

The two-state and Lajtha-Oliver models are compared for identical values of all the parameters. The differences are small but clearly there. The Lajtha-Oliver model changes faster with dose rate because it permits accumulation of damage. Two cases of each are shown, corresponding to high-rate limits that are the same as the one-hit, two-target and two-hit, one-target equations of target theory.

Theoretical Split-Dose Effects

Sometimes greater differences between models can be found for the split-dose effect. It proves convenient in analyzing experimental data to put the predictions of the models in terms of S_1 and S_2 , the survivals to the two doses given singly (discussed above), and S_0 the survival to a single dose equal to the sum of the two that were split. The two-state model predicts

$$(S_1 S_2 - S) = (S_1 S_2 - S_0) e^{-t/\tau}$$

while the Roesch model predicts

$$\ln(S_1 S_2 / S) = \ln(S_1 S_2 / S_0) e^{-t/\tau}$$

where, for both, t is the inter-fraction time and τ is the mean recovery time.

These two equations give quite similar numerical results when $S_1 S_2 / S_0$ is not very large. This is shown in Fig. 4. Roesch's equation suggests that one should plot $\ln(S_1 S_2 / S)$ vs t on semi-log paper; his theory predicts the result will be a straight line. The mean recovery time can be determined from the slope of that line. Figure 4 shows the straight lines for a large and for a small value of $S_1 S_2 / S_0$. The other, curved lines in the figure were

obtained by using the same parameters to calculate S from the two-state equation and then plotting the result in Roesch's manner. The two models are not very different when $S_1 S_2 / S_0$ is small. The statistical uncertainty of most split-dose data would make it difficult to choose which fitted the data better. When $S_1 S_2 / S_0$ is large, there is enough curvature to the two-state curve that one should be able to distinguish whether data fitted it or a straight line.

Figure 5 shows some examples of split-dose data obtained by Bryant for the green alga, Chlamydomonas reinhardtii, for exposure and recovery under either air or nitrogen. Chlamydomonas is a good organism to use for these kinds of experiments, because it has a long period (nearly 12 hours) in its mitotic cycle during which its radiosensitivity does not change. The data are plotted as suggested by Roesch's equation. We interpret the data as all lying on straight lines that have the same slope. Equality of the slopes means that the mean recovery time is the same for all of them. In other words, exposure and recovery under different gases (the "oxygen effect") does not affect the recovery process in Chlamydomonas, it affects the initial amounts of damage.

Fig. 5 Split-dose survival, S , for C. reinhardtii for time, t , between doses. $S_1 S_2$ is the maximum survival reached (determined in the present analysis, not in the reference).

(O) 10 and 11 krad in air, recovery in air
(Δ) 30 and 25 krad in N_2 , recovery in air
(Δ) 10 and 11 krad in air, recovery in N_2
(◊) 30 and 25 krad in N_2 , recovery in N_2
Bryant (1968). Lines drawn for 35 min mean life. Note broken scale of ordinates.