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RADIATION WORKER PROTECTION BY EXPOSURE SCHEDULING

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□ The discovery of the protective adaptive response of cells to a low dose of radiation suggests applications to radiation worker/first responder protection. Its use in cancer radiotherapy has been discussed in a separate publication. This paper describes simple changes in scheduling that can make use of these beneficial adaptive effects for protection. No increase in total exposure is necessary, only a simple change in the timing of radiation exposure. A low dose of radiation at a sufficient dose rate will trigger the adaptive response. This in turn will offer a considerable protection against the damage from a subsequent high dose. A simple scenario is discussed as well as a brief review of the experimental basis of the adaptive response.

INTRODUCTION

The recent tragedies in Japan have focused the attention of the world on safety and recovery from major disasters. In particular, the nuclear reactor failures have raised again the public fear of radiation, both rational and irrational, while the bravery of the technicians at the Fukushima Daiichi plant complex has earned worldwide admiration. In the past, there has been insufficient attention paid to improving the safety of workers who may be exposed to increased radiation levels due to emergent conditions. This note attempts to partially address this oversight. Japanese researchers have performed many of the basic experiments that have demonstrated an adaptive response to low dose radiation (Miyamoto and Sakamoto 1987; Sakamoto 1987; Takai 1990; Yonezawa, *et al.*, 1996; Hattori 1998). As we shall argue, these results together with others can be used to improve worker protection.

We propose that this adaptive response of cells to low levels of radiation be utilized to reduce cell damage by intelligent scheduling, a process termed the **predose protocol** or alternatively **exposure scheduling**. Essentially, prior to an extended planned occupational or emergent exposure, a worker is exposed to a low dose at the site and then retires for a given time period of zero exposure. He then returns for the remainder of his allowed exposure. We do not advocate any increase in the presently allowed total exposure limits nor do we support the idea of hormesis in general. The supporters of the use of the standard Linear No Threshold (LNT) rule that the probability of cancer induction is proportional to the

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total absorbed dose should find no fault with our suggestion. The open question that cannot be answered at present is how much extra protection our protocol yields, both by reducing the incidence of cancer and increasing latency. It could be quite substantial.

There have been many experiments performed which showed that an exposure to a low radiation dose initiates a protective response in cells. Many repair genes are up-regulated by such a low dose. Once this process is well underway, the affected cells can more successfully repair the damage from any subsequent high radiation dose. Cells have many natural repair mechanisms and a low predose of radiation serves to trigger them without doing extensive damage to the cell. This effect has been well demonstrated and the modulated genes identified.

The predose protocol consists of exposing the individual to a trigger dose and then removing them from any radiation exposure for 12-24 hours, called the activation time, to allow the adaptive response to fully engage. Then the individual is allowed to reenter the radiation area with a normal schedule until their allowed integrated dose is achieved. This unusual proposal is based on many experiments done on samples from cell cultures to complete animals to be described briefly below.

BRIEF REVIEW

A typical experiment involves measuring the effects of irradiating a test sample with a low predose, in the range 1 - 100 mSv, and then after the activation time, say 12-24 hours, exposing the subject to a much larger dose of radiation. The resultant effects on survival, cancer incidence and latency is then compared to a sample that had only the large dose. The predose group is found to suffer less damage even though they have been exposed to slightly more radiation. The degree of improvement depends upon details such as the dose rates, total dose, cell type, etc., but there is always an improvement. A review of these experiments has been published (Brooks 2003; Cohen 2002; Mitchel 2010). A large compendium of papers on low dose is available (Low Dose Site). A few such experiments will be briefly described. These experiments are not designed to mimic the typical worker exposure but to study the adaptive response. For calibration note that a dose of 1 mSv roughly corresponds to the absorption of one Co60 gamma ray photon per cell.

In experiments performed on mice (Mitchel 2002; Mitchel 2010), a Co60 gamma dose as low as 10 to 100 mSv protected cells against neoplastic transformation by a subsequent large acute radiation exposure of 4 Sv. Surprisingly, a single pre-exposure of 1 mSv also reduced neo-plastic transformation by factor of 3-4 below the spontaneous rate. Pre-exposure doses ranging from 1 to 100 mSv resulted in essentially the same reduction factor. The effect of a predose on the lifetime of mice was also measured. The average lifetime of a control group that was not irradiated was

727 days. The lifetime of the group that was given 1 Sv of radiation was 486 days. The predose group was given 100 mSv and then after 24 hours a second dose of 1 Sv. Their lifetime increased to 578 days, again demonstrating the protective effect of a predose as well as the increase in latency.

Yonezawa (Yonezawa *et al.* 1996) subjected 3 groups of mice to full body radiation and measured the survival percentage after 30 days. The unexposed control group had a survival rate of 100%. For the group exposed to 8 Sv the survival rate was 30%. For the group exposed to a predose of 50 mSv, a time delay, and then the identical 8 Sv dose, the survival rate increased to 70%. The survival rate more than doubled for the predose group even though the ratio of the predose to the total exposure was < 1 %.

In experiments performed at the Lawrence Livermore Laboratory (Coleman and Wyrobek 2006), (see also Cregan, *et al.*, 1994 and Heller 2003) human lymphoblastoid cells also exhibited the adaptive response and many up regulated repair genes were identified. A dose of 50 mSv was applied and after a wait of 6 hours, a much higher 2.0 Sv dose was applied. It was found that chromosomal damage was reduced by 20-50 % compared to cells with no priming dose. At U. C. Davis (Goldberg, *et al.* 2004) en vivo genetic activation experiments were performed on healthy human skin plugs and resulted in similar protective results for the cellular adaptive response to a low radiation dose.

Rodgers and Holmes (2008) showed that a low dose (~ 100 mSv) delivered to mice at a very low dose rate over several weeks caused little detectable damage over the control presumably because the cell repair mechanisms had sufficient time to act. The same low dose delivered at a high rate, over ~20 minutes, caused measurable damage. A subsequent high dose of ~1.5 Sv was given to a group of mice after a 24 hour delay following the high rate predose and compared to a group subject to the same high dose without the predose. Using a micronucleus assay, the mice given the predose suffered considerably less chromosomal damage 24 hours after exposure than the ones without the predose treatment. Similar experiments with similar results have been performed on canine cell cultures (Blankenbecler 2010) and modulated genes identified. This reference also discusses trials on canines (with owners consent) of the use of the protective adaptive response in radiation cancer therapy. Canine cancers are interesting because they occur naturally and have types, variations and chemistry very similar to human cancers (see for example, Erickson-Miller et, *et al.*, 2000). The possibility of using the predose protocol to reduce the bad side effects of chemotherapy has also been discussed (Blankenbecler 2011).

Further experiments would be very useful in fully describing radiation effects and in particular, its time dependence. For example, experi-

ments that involve a predose followed by a series of high dose exposures spaced at ~24 hour intervals to test the duration of the adaptive response would be very helpful. The useful duration is measured by the lifetime of the repair proteins, not the lifetime of the gene modulation. With such data it will be possible to truly optimize our proposed scheduling protocol. Even with the present data, radiation worker protection can be much improved. Note that our proposal does not use chemicals or drugs that may have unknown side effects and require extensive safety testing. The biological effects of radiation are one of the best studied harmful agents. Radiation certainly causes genetic changes and most probably a reduced lifetime on average. Workers are presently exposed to radiation above natural background levels up to a total dose limit per year. However it is known that the ultimate damage to cells is dependent upon both the schedule of exposure as well as the integrated dose. Further study of the time dependence of the cellular adaptive response promises to yield methods that can reduce this damage. Carefully designed clinical trials are needed to access the risk of the predose protocol compared to the present total dose limit by directly measuring and comparing the degree of DNA damage for both single and double strand breaks. It is not our purpose here to present a fully developed design for such clinical trials.

For the following discussion it will be assumed, based on the presently available data, that a predose threshold value of 1-2 mSv will trigger the adaptive response. However, in certain circumstances, a higher predose of 10-20 mSv may be appropriate. The choice of trigger value is anticipated to be situation dependent.

Scenario: Our predose protocol can be best illustrated by a simple scenario. Consider a nuclear accident such as a runaway reactor in which technicians must enter a high radiation area to control the reactor or make repairs. The technicians are divided into two teams. Both teams enter the radiation zone. One team is only allowed to absorb the chosen trigger predose, say 1–2 mSv, before they are removed from the radiation area for the chosen activation time. This allows the adaptive response to fully engage. This team is then allowed back in to replace the workers who were left to deal with the accident. By shuffling the workers to make full use of the adaptive response, it will be possible to reduce the total damage done by their integrated radiation exposure.

If a long term emergency requires that several teams be used and then each retired after reaching their exposure limit, the first day of exposure for a new team should be limited to the predose value. The team then reports as usual after a 24 hour activation period.

The publically available data from Fukushima is not very complete at this time. It has been reported that the radiation dose rate in one of the control rooms was 0.15 mSv/hr. Thus the lower recommended predose of 1-2 mSv can be acquired in 8-15 hours. The reported rate was hundreds

of times higher near the reactors. For example, at a rate of 100 mSv/hr, the time required to acquire the lower predose value is only 1-2 minutes whereas to achieve the higher predose value a time of 10-20 minutes is required.

CONCLUSION

In summary there are very compelling pre-clinical data that shows that additional protection can be offered to workers and first responders through the use of the **predose protocol** in the event of nuclear accidents or terrorist acts involving radiation exposure. However there is a clear need for more data aimed specifically at exploring the protective function of a low dose of radiation since this is likely to be a complex process. While there may well be additional mechanisms in addition to the gene modulation described above, the net effect is protective. These experiments need to use radiation levels and time intervals that would be relevant to such events. We again stress that we are not proposing any increase in total exposure, only the proper control of the timing of the exposure.

There is an increased probability of radiological events in the future, due to accidents and terrorism. Even with the present state of knowledge, additional protection can be offered to the technicians/first responders charged with handling such disasters. The cost of the predose protocol is very low and involves only intelligent exposure scheduling. To fail to offer all possible additional protective techniques to radiation workers and first responders would be unconscionable.

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