

## Low Dose Radiation Conference Notes

October 2, 2018

8:00A

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Alan introduced Doug Boereham. Doug said that his job today is to keep people on time. The first guy to speak today will be Tony Brooks who needs no introduction. Tony will give a presentation for Biological Effects of Low Dose Radiation. Nuclear weapons were a part of Tony's early life. He was born in St. George, Utah. The sky would light up behind the D, and then we could count the seconds until the ground would shake. Then we could figure out how far away the blast had been. They shot over 100 bombs above ground on the test site. They tried to shoot the bomb so that the fallout would go North and to the east, to where Tony lived.

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They normally planned it so that the fallout cloud would take a while before migrating over towns, however there was one instance with a bomb named dirty Harry that went over St. George, very quickly. In school, Tony studied how  $^{137}\text{Cs}$  enters the body through the food chain. They tests Cs in milk and in cows and in people. Tony even measured himself, and he had some of the highest quantities of Cs. Cs is one of those things that accumulates in the predators at the top of the food chain, Tony was a poor student and so he accumulated a lot of it. Tony worked with Dr. Roger McClellum. Roger wanted him to study Dogs to see if that radiation induced chromosome aberrations. They studied  $^{241}\text{Am}$ ,  $^{239}\text{Pu}$ ,  $^{252}\text{Cf}$ ,  $^{60}\text{Co}$ , and  $^{144}\text{Ce}$ . He inspected the Aberrations per cell versus the Dose (in Gy). Then Tony went on up to PNNL.

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Tony started working on a project working with rats that were exposed to radon. Tony also worked on the BEIR IV report. He said that for the most part, he thought that it was a great report except that one sentence that somebody added stating that "aside from smoking, radon is the second largest source of lung cancer". Tony showed a graphic which showed the Lung cancer deaths versus Radon exposure, for smokers and for radon exposure + being a smoker. Apparently smoking resulted in a much higher number of deaths than radon exposure, but the effect of radon exposure was even more dramatic for people who were also smokers.

8:12A

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Tony worked in a program to investigate the effects of Low Dose radiation. There were three effects that overlapped: Adaptive response, Bystander effects, and Genomic Instability. Tony knew about bystander effects in which one cell gets damaged, and informs its neighbor. Then its neighbor gets it eliminated, apoptosis. He put some  $^{239}\text{Pu}$  O<sub>2</sub> particles into some Chinese hamsters. They had large particles and smaller particles. Apparently, the aberrations per cell was definitely effected by the radioactive particle size. The smallest particles was the best way to create cancer. Genomic Instability can be demonstrated in some strains in mice. There are some mice that are resistant and some that are sensitive. What happens is that following damage, the cells must go through a number of cell divisions before the cells go malignant.

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What came out of the BEIR VII and low dose research, we know of these three effects but we don't know how they effect things. Looking at fetal radiation and coat color change, there are some mice where you can change the color of male avy mice any color by giving radiation to the mother. The thing is, we now have a bunch of additional biological endpoints now that we can study. Systems biology is one of the things that we are going to have to start studying. LNT is effectively dead, and radiation is a poor mutagen. All of the three effects mentioned above provide resistance against radiation damage. Tony enjoyed his career as a radiation biology. He even named his dog Sievert. There are no time for questions.

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Doug said that Marijuana is about to be legalized in Canada in about two weeks, so you can expect a lot of research in Marijuana smoking and Radon exposure. Next we have Sujeenthar Tharmalingam, who will be talking on Molecular Biology and Mechanisms of Action. He wanted to summarize the literature on Low Dose Radiation. He took a look at the Pub Med repository and included only Mammalian studies and those with total absorbed dose below 500 mSv. In the end, we had 320 studies left. He decided to organize the data based on the molecular endpoints. When he looked at apoptosis, about 40% said that radiation kills cells, and 40% said that radiation didn't kill cells. What he realized that this effect depended largely on what sort of cell was being inspected. He thinks that we are okay because the body has multiple levels of protection against LDR. There is DNA damage repair and signaling proteins, at the cell level there is apoptosis, and at the tissue level there are bystander effects, then at the individual level you cancer and others.

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DNA damage is linear between 20 mGy and 100 Gy but DNA damage is untraceable at low doses. He showed a study that showed the effect on hybrid human cells. What happens, that LDR results in prevention of DNA damage. With LDR you have single strand breaks. Then you have multiple enzymes that show up to fix the break. Beyond that there is apoptosis. More concerning is the double ended breaks, but there are a lot of enzymes that are used to try and fix those issues. At low doses you have Homologous Repair (HRR), which is high fidelity with a low chance of errors. The NHEJ repair mechanism which is somewhat risky and can result in mutations, this is only used however in result to high dose rates. DNA repair systems trigger cell death (apoptosis) if DNA damage is irreparable.

8:33A

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Senescence is prolonged cell cycle arrest due to chronic LDR exposure induces senescence in certain cell-types. This concept is a long-standing cell cycle block. It basically allows the cell additional time to try and fix itself. The cell will remain metabolically active. This mechanism is usually used on very important cells such as bone marrow stem cells. We also see that LDR exposure does sort of train the responses of the cellular systems and antioxidant defenses, resulting in increased radio-resistance. There are multiple mechanisms which should protect the cell from subsequent damage, an adaptive phenotype. What we have is probably epigenetic memory. You can have a Gene Expression and also a Gene Expression that is blocked. This is a type of memory that a cell can employ. Also, you can have miRNA which is another epigenetic mechanism. Also there is the bystander effect, where an irradiated cell informs an un-irradiated cell.

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When a cell informs its neighbor of radiation damage, it informs neighboring cells, which then put up their defenses to try to reduce damage to those cells. LDR mediates tissue level defenses against cancer via immune system modulation. It enhances immune mediated selective removal of tumorigenic cancer cells. This means that LDR activates the immune system, which improves the antigen presentation, which increases chance of locating cancer cells. Now the additional NK cells have a better chance of removing tumor cells. When you have cancer, it hijacks the immune system. However, LDR suppresses cancer inflammation which shuts down the immune system. If you give LDR to normal cells you get LDR adapted tissue, which is more protected from future carcinogens. We irradiated mice with 4 Gy and over 4 weeks these mice will develop cancer. Weekly CT scans were given 10 mGy/scan for ten consecutive weeks. The CT scans increased lifespan by 8% which was statistically significant.

8:43A

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There is a hierarchical set of radiation defenses within the body. Conclusions, there are some new paradigms available, but he is out of time. There is time for a question or two. Question/Comment: He wanted to expand one point that is repair and removal might not be 100% efficient, and it is the escape of those cells that causes cancer.

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The next speaker is Randy Jirtle. He will be speaking on Radiation INduced Epigenetic Changes. Randy said that he hasn't been to a radiation conference in the longest time. He thanked Tony for taking the time to have lunch with him way back when he was starting work. We did a study where we showed again that low levels of ionizing radiation showed adaptive responses. The basis for hormesis, is based upon epigenetic effects. What is epigenetics, it is the study of heritable changes in gene function that occur without a change in the sequence of DNA. If you think of DNA as the hardware of your computer, then the epigenetics is effectively the software that runs on that computer.

8:49A

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For every problem in a given discipline of science there exists a special ideal for its solution. The Agouti Sisters are brought up, these are mice that are genetically identical. The only difference is what the mother ate while in-utero (the mice have completely different colors and sizes). Randy said that if you don't get the idea of how epigenetics works at this point, there is probably no hope for you. The Fetal origins of Adult Disease susceptibility. There was a gene in these mice that they would selectively activate, which resulted in a different colored animal that was obese.

8:59A

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The cell that was activated turned off the animals instinct to stop eating when they were full. The obese mice were unhealthy and they also got diabetes. They controlled the diet of the mother mouse. In the control group, there was a natural spectrum of different colors of mice. In the experimental group, they gave a diet that included supplemental non-methyl groups (e.g. folic acid), which resulted in a vast shift towards more brown haired mice (which were healthier). The diet of the mother during pregnancy apparently resulted in changes in disease susceptibility in the mice as adults. He has a background in radiation effects on the radiation epigenome. He had studied chemical effects on the epigenome, but he wanted to know if LDR also had an effect on the epigenome. Again, he used the Agouti Mice. They would irradiate the offspring at the state of very early embryonic development. At the time they irradiated them, they were irradiating embryonic stem cells.

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A graphic was put up that showed the ratios of brown to yellow mice based on the dose of radiation given in-utero. With increased doses of radiation, what we saw wasn't an increase in the number of yellow mice, we saw a reduction in the number of yellow mice. What we ended up seeing a positive adaptive response to radiation. Now as we started to go up to higher levels of radiation, the positive response dropped back down to control levels and then further down at even higher levels. The conclusion was that low doses of ionizing radiation increase the incidence of brown offspring by enhancing DNA methylation. Thus low doses of X-rays induce a positive adaptive response in these mice by altering the epigenome.

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If this wasn't a fluke, then we should be able to mitigate the effect of ionizing radiation by introducing antioxidants. Compared to the control group, there was a huge increase in the number of brown mice resulting from ionizing radiation, however once antioxidants were introduced, dropped the number of brown mice back down to the levels of the control group. Antioxidants negate the increased DNA methylation and block the positive adaptive response. The term Hormesis is from the Greek hormaein which means "to excite or stimulate". Questions, do other frequencies of EM radiation and high energy particles also alter the epigenome. What are the signal transduction pathways that link the formation of ROS to altered DNA methylation. Does low dose ionizing radiation alter the human epigenome. Is the LNT model potentially appropriate for estimating human risk to low doses of ionizing radiation.

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Time for one question... Question, have you ever considered using doses from Radon in your studies. Randy said, yeah I thought about it and it would be very interesting. Now people don't like hormesis so it was hard enough to get this published, but it is likely that people would be even less likely to want to see a paper of this nature with Radon.

9:06A

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Julian Preston will be the next speaker. He will be speaking on Using Mechanism of Action to Reduce Uncertainty in Risk Estimates. His presentation is not meant to be a critique of previous presentations, but to provide a framework to build on the things that we have just heard. He is particularly interested in the research outcomes, of how to use specific information to reduce uncertainty of risk estimates. He will talk about a framework here which might aid people in this respect. He would also like to note that

the LNT hypothesis, is just that, a hypothesis. He likes the L, he agrees with it, it is the NT part that he doesn't agree with. The extrapolation is the Achilles heel of risk assessment. We are going to use below 100 mGy as the low dose rates or ( $< 5 \text{ mGy / hr}$ ) to look at cancer risks.

9:10A

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The calculation of radiation risk estimates for cancer and non-cancer diseases relies almost exclusively on epidemiological data from radiation exposed populations, especially for cancer from the Japan atomic bomb survivors. A number of these epidemiological data sets still have a large number of uncertainties. We will begin by focusing on extrapolation models. For cancer, extrapolation from effects at high/median doses to predict effects at low doses is currently accomplished using the LNT model. We heard a lot of data over the last day and a half, but the question is the data fit for the purpose. How do we use this data for risk assessment, particularly cancer risk assessment. Using the epidemiological approach, you will never be able to answer the question of what will be the response at low doses. You need to be able to find a way to use the biological data. Even the million man project, won't be able to resolve these issues.

9:13A

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He said that typically, we collect bucket fulls of data and throw it at the problem, but he said that it is much more effective to collect a single thimble full of data if it is for the express purpose to fill in the gaps. Unfortunately, we have lots of data, but this data isn't fit for answering this question of dose-response. The question is how can you use modeling approaches to combined epidemiology and radiation biology. He came up with this recent paper which describes the concept of adverse outcome pathways. An adverse outcome pathway is "an analytical construct that describes a sequential chain of causally linked (key) events at different levels of biological organization that lead to an adverse health effect". A key event is defined as "an empirically observable precursor step that is itself a necessary element of the mode of action, or is biologically base marker for such an element."

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He showed off an example of a generalized adverse outcome pathway. Molecular interaction -> Cellular Response -> Organ Response -> Organism Response -> Population response. For assessing the risk associated with LDR, you have to identify one or more of these adverse outcome pathways. AOPs and Chemical Exposures. For chemical exposures there is quite a lot of data already available. There are programs on this specific topic, mainly through the OECD. Mostly these are for non-cancer endpoints, but it does show that this process is viable. Use of AOP/KE data in dose response development. The generalized approach is to develop AOPs and their associated KEs for specific radiation-induced adverse

outcomes (cancer or non-cancer) and use these KEa as parameters in Biologically-Based-Dose-Response (BBDR) model. The way forward. This is the framework, to advance the proposed approach, research programs need to be based on the AOP/key event approach or target research. BBDR models need to be developed or current ones enhanced to be able to fully utilize integrated epidemiology/biology approach.

9:23A

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There was a recent review "Can radiation research impact the estimation of risk?" which was published by Julian himself (in the International Journal of Radiation Biology 93:1009-1014, 2017). A question was pointed out that based on the actual gene that is enabled, it may be something beneficial (hormesis) or detrimental. So we have to look at the overall result for humans.

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Next is Alia Zander who is covering "how fractionation affects ionizing radiation risks". A major question is how receiving a same dose of radiation over a long period of time versus an acute dose. This topic is studied world wide with a range of different results. The original estimate from UNSCEAR was 1.2-2.85, but was later retracted. SSK gave a DDREF value of 1. There are a number of radiation studies, In vitro is nice and controlled but is not physically accurate. Control experiments with rats does allow ease of genetic manipulation, but these are not the species of interest. Finally, with the species of interest, there are lots of confounding factors, lack of ethnic diversity, small sample size and mostly acute exposures. She believes that you need to use all three approaches in an integrated form to come up with a conclusion. She will focus on the Janus Tissue Archive, which contains a huge number of mice tissues which were exposed to different levels of ionizing radiation.

9:31A

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The Cox proportional Hazard Model (the most used model). The benefits are that it is the most popular model for survival analysis. It allows for multivariate survival analysis and also stratification to control for nuisance variables. To begin our analysis, we did a control analysis. These experiments were designed to be compatible and comparable against each other. The control analysis comparison provided this basis. The control group was carried over to where the irradiation would take place, but then not irradiated. Now we can look at the gamma irradiated mice. The mice were tracked throughout their entire lives, then they grouped them by what finally killed the mice. Looking at age at death, the control group mice all lived to a longer age than the irradiated mice.

9:35A

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At higher doses, the mice died much more quickly. By plugging these values into the Cox prediction model shows survival probability versus time. As dose increases, we see that fractionation of dose does increase the chance of survival. Basically as we increase dose, fractionation does increase your chance of survival. Base model robustness checks, and it turned out that it was a robust model. Conclusions: Janus data from separate experiments can be combined for one large analysis. Fractionation of gamma irradiation significantly decreases the death hazard in mice. Neutron irradiated mice will be analyzed.

9:38A

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Next we have Stephanie Puukila to speak. Her presentation is "The influence of dose rate on lung cancer induction from inhalation of Beta-Gamma Emitting Radionuclides". The inhalation toxicology research institute, did many life-span studies on beagle dogs from 1967-1991. Beagles have long life spans, they have similar instances of cancer and similar breakdowns of cancer as humans. They exposed the animals to a variety of different radionuclides. The focus of this presentation is on choosing an appropriate dose rate for the experiment. One major limitation of this study was the number of dogs used, there were 52 controls and around 100 exposed to each of the radionuclides. This data is on-line, look at the "Lovelace Institute Tissue Archive".

9:42A

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During these studies, ITRI publish reports, the final one was published in 1994. For the full results, look at Kris Tomaes poster in the poster session. Looking at a graphic, low dose rates were almost the same as the control group, however the medium and dose rate groups died much more quickly of lung cancer than the dogs in the control group who died of lung cancer. At high dose rates, the dogs died very early of pulmonary injuries. For  $^{90}\text{Y}$ , the different dose rates are effective, whereas the different dose rates used for  $^{90}\text{Sr}$ , were not effective as there wasn't much variance between the three data points. Time for questions/comments. One of the challenges we have is defining a high dose rate versus a low dose rate. But he is wondering how we can address that in humans where we have a large number of different types of cells. Tony will answer. Indeed the lungs are a complex organ and there are a lot of cell types, we focus on epithelial type 2 cells, the cell turnover there is about 30 days. We tried to describe dose rate. So we tried a lot of different things and what we finally settled on was the effective half-life. Half would be given at a higher dose rate and half given at a lower dose rate. We know that each cell type in the lung is unique, but that is how we did this particular study. What Dr. Robby did was to take the average dose, which was the total dose divided by the latent period. The problem is that latent period is not a measure of dose rate. Roger would like to speak. We put together a very distinguished scientific advisory committee. At one of our sessions, Roy Albert, said our research won't have an impact because we can just go down a list of all the radionuclides. He was the individual who pushed us towards using a consistent biological vector (silica particles).



9:52A

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It was a reasonable hypothesis then, but you have this challenge in which scientists are used to working with a constant dose rate, or with fractionation. However, in the real world, things are not that simple. However, if we torture the data enough, we can come up with some different endpoints. If we continue to tear apart the work that Otto Rabbe worked on, we can come to an understanding of the Pathogenesis.

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BREAK

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10:19A

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Nick Daniak is the next speaker. He will be speaking on "Understanding Paracrine Signaling and Stem Cell Function through Computational Modeling". He will be getting into the signaling that happens within the bone marrow. The mejuary portion of the bone. This puts bone marrow cells in close contact with the bone surface. There is a large number of capillaries at these locations. There is inter-cellular signaling between different cell types. Signals can go up to 700 um, which is quite a ways. Here is an endosteal Niche, where is new bones are formed. Within this there are osteoblast a different cell, which work together to form bones. Stem cells as well release vesicles. Also, there is perivascular niche.

10:24A

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When cells pass through the venus system (into the blood). They actually have to pass through other cells. Stem cells reside throughout the bone marrow. How do cells signal each other, one is through exocytosis, horemones. proteolytic cleavage of surface molecules (EGFR). Gap junctions (ROS, DDR mediators, etc). If we have an irradiated cell, extracellular signaling can cause changes in neighboring cells. On gap junction communication, there was a paper that looked at transmission distance. He assessed propagation distance within a 100-um radius around the intra-nuclear alpha particle impact point in confluent human fibroblast cultures. Mean distance ranged 20 - 40 um. This isn't enough to answer his question of can these vesicles move. A picture of a TEM of a gap junction is shown. Gap junctions form within a colony of cells. This topic was captured by Tavassoli and Shiaklai back in 1979.

10:29A

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He was interested to know if signals were soluble or not. He used freeze fracture electron micro-graphs. There were vesicles with pits. These vesicles were heterogeneous in size ranging from 0.1-0.4 um. These were called shed vesicles. He thought the idea was great, but the world didn't receive it the same. Nowadays, micro-vesicles are quite a thing and are researched quite a lot. Upon inspection of the vesicles, we found out that they are very hardy, they are sealed. These vesicles do express the growth factors. It was determined that not only do vesicles transmit a signal but they can also concentrate a signal. In addition, we found IR induces Fas (TNFRSF6) expression on micro vesicle surface of SW620 cells.

10:34A

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Shed vesicles are derived from the plasma membrane. There are also exosomes, which are smaller than the micro vesicles (MV). What do vesicles do? well they can deliver signals. A picture is shown where DNA and RNA are being delivered into the appropriate spots of other recipient cells. They exposed a full thickness skin graph to alpha radiation, and they looked at rates of apoptosis. He used a program to model this experiment. The calculation used a diffusion length formula. The results were that he found a straight-line curve. The diffusion length of 1.27 mm for a MV is sufficient for transmitting information perhaps relating to radiation exposure.

10:38A

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A question was asked about the DNA transfer, was it a mitochondrial DNA transfer or cellular, he said that it was a cellular transfer. Next speaker will be Dmitry Klokov. He will speak on Low-Dose Radiobiology Program at Canadian Nuclear Laboratories: Past, Present and Future. He will start by talking about the Canadian Nuclear Laboratories. Like Hanford, this lab is located in the middle of nowhere. Most people know of us as AECL, but now we are CNL. Chalk River is the birth place of international Radiation Protection (RP). During WWII the UK nuclear lab moved to Canada in 1942,. It joined the Manhattan project and moved to the Chalk River. Then they came up with the needs for agreed RP norms. It came up with the first set of RP standards.

10:42A

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Early studies (1945-1975) were pioneering studies in LDR. There were studies of Mutagenic effects of radiation in bacteria, mammalian cells, and fish. Epidemiological studies/new quantization approaches were also done. Finally, there were low does studies. Newcombe (1973) did also talk about the "Harm" vs. "Benefit" argument. Between the 1970s-2000s, Ron Michel battled with management until he was

finally able to build a low dose facility. The area is 30 m long. There is one location in NORway and One in Japan that can do similar studies. He did a series of studies in mice. LDR delays the onset of tumorigenesis in mice in vivo. An increase in tumor free time was observed for ostersarcoma and lymphoma.

10:46A

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These are highly cited papers, but Ron Mitchel never inspected the mechanism for these results. When Dmitry started working at the lab, he wanted to know if DNA repair was involve. DNA double strand break repair is not activated. Also other types of DNA repair pathways are activate in mice at about 10-100 mGy. So how does it go from DNA damage to cancer, this is a complex process. This system approach started in 2014, and is ongoing. The biggest factor contributing to cancer is aging. We decided to look at aging as a surrogate for cancer endpoint. LDR suppresses cellular aging in vitro. Doses of 12.5 and 100 mGy were used and it did delay aging onset. There are other acute gamma LDR effects. LDR in vivo: does not enhance aging markers in mice in vivo, activates the immune system of old, but not young mice, enhances the Immune Checkpoint Therapy efficacy in mice.

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LDR in vitro: partially reverses aging-related loss of stem cells. This is true for muscle SC, mesenchymal SC and endothelial SC. This may have a use case for regenerative medicine. To understand the holistic picture, we decided a number of years ago to try an track all of these changes within a single model. We decided to use cancer mice models. We have some mice which are bred to be naturally predisposed to cancer. We exposed mice to gamma radiation and radioactive water HTO. There are a bunch of endpoints that we want to investigate from this, but this research is ongoing. In another test, we expose normal mice to gamma and HTO for 1-8 months at various dose rates and we have a lot of endpoints to look forward to.

10:54A

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For a CBA/J Life span, 66 mGy total cumulative dose, the tritium and gamma exposure were shown. At lower levels of dose lifespans were largely unaffected but as they went up, lifespans were reduced. CNL maintains the worlds longest running low-dose program. CNLs results collectively support the lack of detrimental biological and health effects at low doses. CNL does have a focus on holistic research. Time for Questions: Jerry Cutler, said that you didn't mention thresholds. He said that you saw positive effects at low levels and then at some point things were not beneficial. Dimitri said that the threshold sits at around 200 mGy, as a 2 week chronic exposure.

11:01A

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Panel Session #3: This is going to be moderated by Ludwig Feinendegen and includes the following panelists:

- Antone Brooks

- Helmut Sies

M Ludwig Feinendegen

- Janet Baulch

- Noy Rithidech

Ludwig would like to start by making some comments on Low Dose effects. He showed a diagram of the steps resulting to lethal cancer and the physiological defenses to these steps and the probability of their success. There is a 1 in 50 chance of radiation damage to cells from background radiation. The defenses include, detoxification scavenging, DNA repair, APOPTOSIS, Cell Senescence, Immune Response/Apoptosis, Immune response / Inflammation. A plot was shown of percent protection following an acute low level LET irradiation. There is quite a spread of values from these studies on this plot.

11:09A

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Noy will now speak on "Delayed Effects of a Whole body exposure to low-dose radiation on somatic and germinal cells of mice". These slides show why it is important to cover this study. There is a gap of knowledge. There is insufficient information on late or delayed effects of low-dose radiation (LDR) that are highly relevant to risk assessment. We conducted a study to cover this point and two others. We concentrated on a mouse model and focused on 0, 0.05, 0.1 and 1.0 Gy of <sup>137</sup>Cs gamma rays delivered to mice. There were two portions in this study, in one part we extracted proteins, Cytosolic fraction and nuclear fraction.. The conclusions of the study is that a single dose of 50 mGy does not do any harm to any tissue that we exposed the mouse to. We did also see the hormesis effect in the 0.05 Gy exposed mice but it did depend on the particular tissue in question

11:14A

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Janet Baulch is now speaking on the Effect of Whole Body Radiation Exposure on DNA Methylation in the Brain of the Irradiated Mouse (Poster #1). Not only are we interested in methylcytosine, but there is also 5-methylcytosine that we are interested in. DNA methylation is an excellent biomarker for radiation exposure, even at low doses. Functional relationship to risk is still largely lacking. Furthermore is risk really the correct word to be talking about. Can we use mechanistic data in risk assessment. Carcinogenesis is not the only potential adverse outcome. The CNS is sensitive to irradiation and cognitive dysfunction manifests in radiation oncology relevant and NASA relevant exposure programs. In our NASA relevant studies, we can manipulate methylation levels. Radiation causes an increase methylation. Also, there is a chemical that can be delivered to the mouse after the fact which can restore the mouse back to something approaching control levels.

11:20A

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She would like to throw out a well designed study of the human cohorts included from the Mayak studies. Particularly to see if there is some increase in neuro-degenerative diseases (e.g., Alzheimer's disease). Helmut will now speak. His first slide shows that hydrogen peroxide is the result of ionizing radiation. These oxidants are normal attributes of our daily life. H<sub>2</sub>O<sub>2</sub> was present on earth much more prevalently than O<sub>2</sub> before photosynthesis was common. For low doses below 100 mGy, the low resulting quantity of H<sub>2</sub>O<sub>2</sub> results in oxidative eustress (redox signaling), for high-doses greater than 100 mGy (and the associated higher H<sub>2</sub>O<sub>2</sub>) you have Oxidative Distress (Disrupted Redox Signaling). The adaptive stress responses to low dose are Nrf2 and NF-κB.

11:26A

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There is an interesting relationship between growth factors and H<sub>2</sub>O<sub>2</sub>. At various H<sub>2</sub>O<sub>2</sub> concentrations there are positive and subsequently (at higher doses) negative cellular responses. Now on to questions...

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Two questions to pose to the panel here. We are working to coordinate global low dose research. The question he has is, how many researches here are already collaborating with chemical toxicology here.

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Another question, he cautions people on the adverse option pathways. Because he said that it is an outgrowth of our thinking in carcinogenesis that it is a linear process. We need to broaden that spectrum that Ludwig showed to include more of the other things (outside of radiation). He sees a network up there of hundreds of steps which may lead to the carcinogenesis. Would you consider thinking about this as a network.

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Ludwig said that yes, I have thought about things as a network but I didn't have time to explain that as I went over my slides earlier.

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The low dose effects are on the order of 100 mSv doses in sort doses. Has anybody ever thought about what from an evolutionary standpoint what might create short term doses of 100 mSv.

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Ludwig said that he doesn't think that the body handles radiation stresses specially, its handled by the body in very similar ways to other stresses.

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Helmut said that H<sub>2</sub>O<sub>2</sub> may be used as way to signal information between cells. But where is the boundary between eustress and distress, it may be different based on time and other things.

11:36A

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Janet pointed that there are some NASA relevant doses in the cGy where they see persistent neuro-cognitive dysfunction as a result.

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What we observed in a patient was that three doses in a two week period was beneficial, but a fourth was detrimental. We had to wait a few months before it was beneficial before.

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A question for Ludwig, last week at the CHR conference the results from a European study was presented. They come up with significant excess of brain cancer, at 50 mGy, they came up with a significant increase in brain cancer.

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Ludwig said that he can provide the questioner with the list of the 18 references that he can look at for the answer.

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Question, there was a lot of research on the timing of methylation... If we are talking about radiation, are we talking about good outcomes or bad outcomes, how common is it?

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The speaker said that we really don't know a lot about this. If you turn off a good gene, that is bad, if you turn off a bad gene that is good. The good news is that we now have the sequencing tools to start

inspecting these sorts of effects. We need to find the resources and people to start driving these projects forward.

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Noy said that they did global exposures and that when the mice had reduced quantities of 5-hydroxycytocine they had longer times to develop cancer.

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Janet said that yes 5-HNC is a new thing that needs to start being researched.

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Janet said that the marks we see on the epigenome, all of those get their precursors from metabolism.

11:45A

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For us it has been about 15 years of looking at mechanistic data. Our guidelines have us look at all the data first, human and mechanistic data. Then we look at how that data affects low dose. The guidelines allow us to be linear, non-linear, to use threshold. We also look at if we have a mutagenic mode of action. If you have that data, you use it or you use a linear low dose extrapolation. This is largely based on how the treatment of low dose radiation is handled. In fact our agency has included a default situation where all of the available models for a chemical must be looked at. It is very similar to the treatment for radiation.

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There was a discussion this morning about mechanisms but there was almost no discussion of variability. There as a question if we have thought about things at the population level. His question is where do we go from oxidative eustress to oxidative stress.

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Tony said that we know that there is a lot of variability in all of our genes. All of these measurements that we have made can be pushed around. We had an NCRP committee that was trying to look into genetic variability for astronauts that they were planning to put into space. For the most part there wasn't much genetic diversity except for some people who had a genetic disease.

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Noy said that people are proposing to use a different type of mouse. They are inbred mouse, so the diversity mouse may be more representative of the human population. But the price of this study will be huge as the price of a diverse mouse is about \$60/each in comparison to the price of the inbred mouse \$13/each.

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The immune system plays a huge role in the efficacy of cancer. The guy suspects that it would be more pertinent to study the effect of radiation on the immune system.

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Roger McClellan wanted to ask a question of how many people in the room know a couple of gentleman. He said that he hopes that Dr. Zander knows who those people are as they were critical to creation of those sets of data. He wants to emphasis the importance of those types of data. We are just now seeing the tip of the iceberg with regards to teasing out information from that data. He encourages the use of the Cox ???, We need to preserve this data and to make data more accessible than in the past.

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As a person without a lot of skin pigment. He has a lot of experience with an adaptive symptom called a sun tan. He said that his tan lasts only for about two weeks. But his question is, for these DNA methylations, how stable are the epigenetic changes, do they only last a couple of weeks or are they for much longer.

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Epigenetic changes are very stable, but the length of adaptive responses have not yet been looked at. Ludwig said that it is now the end of session.

11:59A

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Ludwig wanted to thank the attendees and the particularly Allen for this event. Allen is imploring people to pick up lunch and to go and look at the poster sessions while we eat.

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LUNCH BREAK

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1:01P

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Plenary Session #5 : The Role of Modeling in Radiation Protection

Alan introduced Dr. Kathy Higley. She will be the chair of this session. speaking on the following topic:



Darrell Fisher will be giving the keynote address. Darrell's said that way back when, Alan asked Darrell what would be the one biggest change that we could make to improve things. Should the dose limit be 1 mSv/year or should it be 5 mSv/year or should it be something else. Prior to ICRP-26, the dose limit to the public was 5 mSv/yr. In the same publication it also mentioned a dose limit of 0.5 mSv/yr. For historical context (1983 Washington Meeting) this suggested moving towards the 1 mSv/year. The 1985 Paris statement by the ICRP, reduced the limit down to 1 mSv/year. In ICRP-60, when it recommended its occupational dose limit from 50 mSv/year to 20 mSv/year it also reduced the public dose limit from 5 mSv/year to 1 mSv/yr. The ICRP justified that the annual effective dose of 1 mSv is roughly the same as background radiation and that even this level of dose might not be safe.

1:08P

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Essential underlying assumptions for a 1 mSv limit. Future radiation-induced cancer incidence is predictable. Risk of stochastic detriment from low-level, low-dose-rate radiation is known, and in all cases may be modeled correcting from the Japanese atomic bomb survivor LSS epidemiology. The LNT dose response hypothesis holds at all dose levels between 0 and 100 mSv. The additive risk hypothesis holds for the entire lifetime. Another driver for the ICRP dose limit was the idea that the public could be exposed to more than one planned exposure. For example Richland, WA which is located next to a nuclear site (Hanford) and also next to a nuclear power plant. The average background radiation is about 6.2 mSv/year. Nuclear represents 0.1% of the total public dose.

1:12P

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The thing is, once we see that the actual background radiation is over six, then we can see that the public dose limit is actually about 1/6th of the background radiation. What is 1 mSv effective dose. 1 mSv is assumed to be the whole body dose that one might receive from a continuous ambient external exposure rate of about 100 mrem/yr. What is the perceived risk of 1 mSv/year. If the LNT hypothesis is correct, then conservatively speaking, then the perceived lifetime risk associated with a 1 mSv risk is 0.35% increase in cancer. The ICRP rationale for lowering the public dose limit for 5 mSv to 1 mSv per year looks weak because it was not based on citable science. No evidence has been provided over the past 35 year so support the lowering of the dose limit.

1:15P

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The ICRPs stance on the selected dose limit is lengthy and confusing. What is missing behind the 1 mSv public dose limit. Acknowledgment that risks are not known with certainty at exposure levels below 100 mSv. Acknowledgment that epidemiology cannot confirm the assumed risk coefficients used below 100 mSv. Acceptance of contrary scientific findings in radiobiology. Under 40CFR90, the EPA regulates

radiation dose to the public from normal operation of nuclear power plants and other uranium fuel cycle limits. The EPA has select limits that are as much if not more restrictive than the ICRP. EPA set the annual dose equivalent to the public at 0.25 mSv to the whole body. Therefore to comply with the federal limit, site operational limits are usually set to a conservative fraction of that usually a 1/10th. In ICRP Publication 81, for radioactive waste disposal for control of public exposure, the ICRP recommended a dose constraint limit to the public of 0.3 mSv.

1:19P

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It is the policy of the DOE to implement legally limits suggested by the ICRP. As of January 2009, the cost of site cleanup has been high, but in light of these even more restrictive public dose limits, the costs will balloon even higher. The EPA has admitted that the reduced dose limits have resulted in higher costs for remediation. What can we do about this. Darrell suggest that we might move back to the 5 mSv limit, or we might even consider a higher limit in the range of 5-20 mSv, this would have resolved an issue that occurred at Fukushima Dai-Ichi. The ICRP has set the public dose limit too low at 1 mSv. Questions will have to be delayed on this.

1:23P

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John Dunn will give us a presentation on Arguments Against Linearity at Low Doses. John Dunn got a Law Degree, but he isn't a lawyer. He studied law mostly because he wanted to learn about civics and history. No matter what you do, you cant avoid the fact that the government is in your life in some way. The reason that he is here is that somebody knew, that I have been fighting this LNT thing for over twenty years. As a physician, I know all about toxins. I also know that poisons have thresholds of effect and if you know anything about pharmacology, then you know that living things are susceptible to toxins and normally it happens over a threshold.

1:26P

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John said that he wrote this paper as a submission to the health physics journal. The funny text is shown here to emphasize his particular points. This is nothing more than his effort to summarize the results of this conference. The US EPA is on our back about everything. Small particle research is mostly epidemiology research. We are here to talk about the precautionary principle. This is about how we can make the precautionary principle the guiding light for regulation. He thinks that immature people, or people who want power and control are the guiding light. Little people who don't have the tolerance for risk or discomfort are a big part of the problem. For example, most schools these days talk about zero-tolerance on one thing or another.

1:30P

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John would like to talk about the problem of the precautionary principle. The second problem is about what the government activity is about. If you scare the public, then then you can change things by exercising the precautionary principle. He knows for a fact that you cant kill people with small particles. However, the EPA is talking about 350 people per year about dying from ambient small particles. The one hit assumption that LNT is based on, is something that appeared in medical textbooks some time ago. At one point, it was adopted by the entire medical profession. The one hit theory was considered to be a sacred cow. However, here is one big problem, we still don't know exactly what causes cancer. This is nothing more than my summary of Calabrese, Welsh, Segall, and others. His concern is that if we don't start doing some good science we are going to be ruled by the precautionary principle.

1:35P

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What is he going to do about this, the reference manual on scientific evidence. This was published in 1995. You can get a copy of this book for free on the Internet. The third edition was publish in 2011. The reference manual was published because of a decision of the supreme court of the united states. In a Daubert hearing, you don't just have to be a scientist or an engineer. If you propose to testify to court and the jury is going to ask you what sort of science you are basing things on. If you think about it, the Daubert opinion has been adopted by all states. John wants to be shown the evidence for LNT. Dirty Harry said that "a man has got to know his limitations" and in another quote, he said "show me the money".

1:42P

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There is time for one question. There is one comment. He tried to explain yesterday with what he said yesterday about the precautionary principle. It works as long as the consequences on the conservative side aren't worse than than the alternative. There is a guy named Frank Furidi, I show everybody a lecture that he gave to people in Italy. The precautionary principle is a distortion, which leads to the zero tolerance. Realistically, risk management is what it is all about. He wants to know what the risks really are. The next presentation will be by Kathy Higley. She will be speaking on "Radiation Protection, it's not just the numbers".

1:45P

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We had a couple of conversations about background radiation. Background radiation is not uniform. Also, it varies by latitude and longitude as well as temporally. Stepping back into a little bit of philosophy. She would like you to think about the early days of radiation protection. It has been over 100 years since we discovered radioactivity, and people started using it for everything. The picture on the bottom right shows a bare x-ray machine and he isn't shielded. What we see today is that fads follow the science. \*She showed off some radiation bath salts\*. She said that this stuff is really part of our history. As the science unfolded, they were discovering new radioactive elements. At this point, the science had to scramble to keep up. In 1927, we found out that you could cause genetic effects in fruit flies by using ionizing radiation. The industry was also working ahead of the health and safety.

1:51P

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They came up with this radium paint source, that they put on watch dials and on other places. The radium dial painters, experienced some serious health side effects. We know that there is an effect because we recorded it, but one of the radium ladies lived until 107. Science and engineering worked really hard and really fast to unleash the nuclear weapon. And it took humanity to a place where we had never been before. In the process for developing the tools for war, the US was trying to come up with exposure limits. We started lowering the dose limits further and further. In 1957, we set the limit to workers at 5 mRem/year. We have also started protecting the public. The takeaway from this is that our radiation protection has evolved. Managed harm to prevent deterministic effects and manage probability of harm with focus on ALARA.

1:55P

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It seemed like we were really starting to get things understood and then Chernobyl happened. Bruce was talking about the Tetra river and the Mayak workers, but those things were not terribly visible to the public. Chernobyl on the other hand was very visible to the public. It didn't matter that it was a different design than what we use, and it didn't matter that they did some stuff that they weren't supposed to do. So yeah, some bad stuff has happened, but we need to keep in mind that there have been some tremendous benefits to using radiation. For example CT scans work very well. We also are realizing some unique capabilities for nuclear to be used out in space or also for addressing climate change. So there can be a role for nuclear if we can get over the fear that we have.

1:58P

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We know that there is a point with higher doses that really bad stuff definitely happens, and then we also know that there is a really low region where we can't really be sure what we are seeing (100 mSv). Below that, we have this area which encompasses natural environment and diagnostic procedures.

People who use radiotherapy go above this 100 mSv limit, but for health reasons. The Navajo Nation for example spent a bunch of money trying to re-mediate the existence of uranium in their dirt. However, there is all this focus on Uranium and Radon, realistically the largest health concerns for them are actually because of poor drinking water.

2:02P

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So what do we do. The underpinnings of our radiation protection is not only based on the science, but it includes experience values and social and ethical principles. There is still however this issue of social ethical principles and values. Some practical steps is realistic exposure scenarios. Also, we need to keep things in perspective. Are 100 mGy studies relevant to 0.04 mSv standards.

2:04P

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Question/Comment, she was on the EPA advisory committee in the 1970's, in that time the EPA set standards for coal plant emissions by looking at the average exposure going in either direction and they said that we can't protect everyone. Now they are applying the LNT to air pollutant emissions. The next speaker is Allen Chan. Allen Chan will be talking on Low-Dose Radiation: Inter-agency Collaboration on PLanning Research Could Improve Information on Health Effects. He is here to present a report that he came up with last year. Before he gets started, he will give the background on GAO. It is an independent nonpartisan agency serving the congress to help improve the performances and ensure accountability of the federal government. Within GAO we are organized into 14 mission teams. He is part of the GAO's science and technology issue area.

2:08P

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Last year he worked with the low dose program. One of the advantages of a GAO report is since we are non-partisan we can get information from lots of different groups and companies. Another great thing about our reports is that we tend to distill the information down to a very low level so that it could even be understood by a high-schooler. Our report was requested by the house committee on science, space and technology. The report was issued in September 2017 (GAO-17-546). There is also a summary page for those short on time (GAO-18-184T). Definition of low-dose radiation. Below 100 mSv (10 rem) according to National Academies 2006 BEIR VII report. We focused on ionizing radiation.

2:12P

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The review was restricted to four settings: operation and decommissioning of nuclear power plants, clean up of sites with radiological contamination, terrorist acts and dirty bombs, ????. For the first objective, the agencies relied upon advisory bodies to make decisions (ICRP, NCRP, and National Academies). Support LNT model, assume risk of cancer increases with every incremental increase in radiation exposure. A number of limits are shown, the public dose limit (1 mSv/yr), the natural background level (3 mSv/yr), and others. Objective 2: Federally funded research on low dose radiation health effects. Seven agencies funded research for low dose research, the DOE and NIH are the largest sponsors (98%). Looking at the trends from 2012 to 2016, there has been a 48% decrease in funding for research. The DOE ending its low dose program is one of the big reasons for this reduction.

2:18P

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In the past there have been some GAO reports, in 1981 and in the year 2000. In our report we made the recommendation that the secretary of energy should lead development of inter-agency collaboration mechanism to determine the roles and responsibilities for addressing priorities for low dose radiation research. The DOE did not concur with our assessment, but recently informed GAO that National Science and Technology Council (NSTC) within the White House will work with agencies to align plans with the low dose. These reports are available at the following location:

<http://www.gao.gov>

A question was if the OMB has been enforcing the data quality act. Allen said that he wasn't sure and that he wasn't familiar with the data quality act. Next is Mohan Doss who will be talking about Radiation Hormesis and Radiation Protection. As a matter of disclosure, he is one of the members of SARI and president of the XLNT foundation.

2:23P

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He is a medical physicist and the three big diseases to worry about are Cardiovascular Disease, Cancer, and Alzheimer's Disease. The first two of these diseases are the largest causes of death in the US. The LNT model presents a major obstacle for performing investigative studies of prevention and treatment of these diseases using low-dose radiation in spite of available evidence. He said that this is not a matter of politics, this is a matter of science. What he would like to do is to pick the best of the best stuff, for supporting the LNT model. In the BIER VII report. He said that the atomic bomb survivor data does not support the LNT model due to a dip in ERR with increases in dose. The Top 3 datasets in support of the LNT model will be discussed.

2:27P

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Cancer incidence in the atomic bomb survivors. In 2017 a publication stated that there is too much uncertainty in these data to guide radiation protection policies, this is not support for the LNT. LNT would not be able to explain the lack of increase in cancer when the radiation dose was increase from 0.2 to 0.7 Gy. Other studies claimed by the NCRP to support the LNT model on closer scrutiny were found to not support the LNT model. There was a publication you can read, "Are We Approaching the End of the LNT Model". He would now like to present the evidence for Radiation Hormesis. There are studies from the 1950's up to the 1990's.

2:30P

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This information is provided in the poster out in the poster session. The BIER VI report said that this effect can be confounded by the effect of smoking. Discussing the lung cancer risk versus Radon. Now on to high doses from Radon. This is a minor study. Of course it increases lung cancers, but it also resulted in some significant reductions to other diseases. If you consider all things together, there is no appreciable difference . These are high doses over a long period of time. There are high doses to some organs but low doses to other organs.

2:37P

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He said that you need to take a look at the total effect of things. It is like letting you kids go off to play soccer and then they come back with bruises. You say, this is the result of you playing soccer, so you shouldn't play anymore. As a result, you may have them watching more TV and perhaps being more obese. So how do we protect people from low doses of radiation. the authority of this in the US is by the EPA and NRC. He said that dose rate is a very important issue. As an example, one pill a day over 100 days is not the same as 100 pills in one day. The atomic bomb survivor data is from an acute dose. The impact of this new paradigm would be to enable study of low-dose radiation for controlling cancer and non-cancer diseases, improving health. Reduce concerns regarding nuclear power renaissance of nuclear power and an era of prosperity. Avoid casualties due to unsafe energy sources. We should abandon the current paradigm and adopt the new one promptly.

2:43P

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Dr. Bennett Greenspan will be speaking on The Case for a Threshold. He was asked to give a talk on the case for a threshold, even though his proposed abstract was the LNT is wrong. So I'll talk about both. LNT claims cancer risk extends down to zero but there has never been evidence to show increased risk

below 100 mSv (10 rem) and probably 200 mSv (20 rem). LNT assumes radiation damage and associated cancer risk accumulate throughout life. Not true, this ignores the repair of DNA damage. Radiation hormesis is real. Many substances -drugs vitamins, trace metals and are beneficial at low levels. Atom bomb survivors had less nonmalignant disease;. The Canadian TB patients had 1/3 less breast cancer. Nuclear power workers have a decreased risk of malignancy.

2:47P

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The case for a threshold. Everything has a threshold (including drugs and vitamins). Radiation is a natural entity of the environment. Low dose radiation is beneficial and high doses are harmful, therefore there must be some threshold at which the situation changes between the two. Based on non-human data with beagle dogs, inhaled plutonium dioxide threshold of approximately 140-400 mRem/yr. Thresholds for carcinogens. Secondary cancers from radiation therapy with a latent period of 5-8 years. There is clearly a threshold of about 200 mGy. Atom bomb survivors show a threshold at about 700 mGy/yr. People who live in high background areas have not increase in cancer rate. In some areas, rates are lower. In terms of treating thyroid cancer with I-131, there is no increase in solid tumors and a slightly increased risk of leukemia above total administered activity of 600 mCi. Conclusions: General principles behavior of radiation as a toxic substance is similar to other toxic substances. Thresholds for development of carcinogenesis are identified. Different tumors exhibit different thresholds.

Thresholds in humans probably range from 0.15-0.70 mSv.

2:54P

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A questioner pointed out that one of the figures included in this presentation included an unhealthy control group and has been superseded by a later variant. Another comment, was that the reason that humans handle radiation okay is actually natural selection, because if humans couldn't handle it they would have died out. Another commenter mentioned using the flourosopic device, and the guy pointed out that he is old and that he hasn't had any issues with his feed. His second comment, is that if you have a safety situation and you have the precautionary principle and a bunch of agencies in this area, then those agencies will start competing with each other to see who can be more careful to the public, so it really is a race to the bottom in a sense. It is true that if you have some data points with two standard deviation error bars, then you would expect 1 in 20 of them to miss. However, he would point out that a fair quantity of data presented to us doesn't meet that criteria.

3:00P

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Norm Dier would like to make a comment on the cost benefit. However, he said that sleeping with somebody else in your bed will give you an additional 0.1 mSv/year than if you sleep separately in two different twin beds. Time for a break.

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BREAK

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3:30P

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Panel #4 : Models of Dose Response Relationships; Moderator David Brenner. The following panelists are involved:

- Jerry Cutler
- M David Brenner
- Darrell Fischer
- Mark Miller
- Kathy Higley

David wanted to start out by showing how hard it is to do a low dose study. They looked at all of the children in the UK who had CT scans, and even so, the error bars still cover zero. He said that given what he sees here, he is surprised at the ways that people have been able to speak on things with such certainty.

3:34P

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Starting with Jerry Cutler, he wanted to try and administer low dose radiation to an Alzheimer's patient. The doctor said that the only thing that he could do was to prescribe CT scans to provide that radiation. After seeing the good results to the patient, the patients spouse also wanted a CT scan to improve his Alzheimer's symptoms. Is the LNT wrong, is it false, what about the scientific method. He will present evidence of scientific threshold. Leukemia data of 95,819 Hiroshima survivors. They have the year and the total number of cases. There are about 48 cases and the number of people were 4 thousand in the first two areas. The mortality is 0.5% of the irradiated people. Leukemia, the blood cells are supposed to

be very susceptible to radiation. He plotted Wally's data, and showed how the number of Leukemia cases increases after the bombs and peaks at about five years after the bombs.

3:39P

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This data was tabulated in UNSCEAR. He plotted this data in log scale and you could see the high radiation areas near the bomb center. And you can see that in the lower regions, there is a reduced incidence of leukemia. He spoke about a pilot study of the LDIR-CT. They are going to be using CT scans to try and treat Alzheimer's disease. Next is Mark Miller. He will briefly go over the origins of SARI. It all started when Fukushima happened. There was too much misinformation and radio-phobia going on. There was little rigor in the news. So they created a website to try and counteract misinformation when they see it. They want to be very concise and accurate with rebuttals. SARI hopes to tap into the synergies that result from collaboration with like-minded individuals.

3:44P

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As Mohan pointed out, there is a booth out there and some sign up lists in case you want to join. Dr. Fontos had some questions from the last session that he wanted to ask, so he can ask them now.

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Dr. Fontos wanted to comment on Dr. Doss's information. He was concerned about the information regarding the Tetra river information from 1994. He said that when one does a literature review, he was surprised that he would miss all of the other literature published of the cohort since 1994. For example, he showed a statistically significant response for this cohort in 2013. And another publication that went out in 2015. So he won't repeat what the cancer risk estimates were, you can go back to the slide. So he would like to recommend that when somebody is going to make pronouncement of pro-ported evidence, that you do a thorough literature review first.

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Dr. Doss came to rebut the comment. He said that there is an issue with the LNT fit of that data. He said that the best way to evaluate equivalent risk is to compare a cohort against a control population, that is what the 1994 report included. Once you guys release a new report of this nature, I would gladly use that new report. He said that he did look at later reports but did not use them for the aforementioned reason.

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David Brenner said that all data sets have some problems, Tony said that he isn't an epidemiologist and said that you need to be really careful to your preconceived notions to not cherry pick things. Tony likes the idea of SARI, but he is concerned that they are going to take that opportunity to point fingers at other people and say that they are incorrect because they have a different point of view. Tony said that

he used to have students come up to him and say, "Dr Brooks, we ran an experiment and it failed. It didn't come up with the result that we were looking for." He joked and said that clearly the test subjects weren't privy to their plan.

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A question was asked of what sort of alternative model might be used instead of LNT.

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David Brenner said that most data these days fit to the tri-linear model.

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The questioner rephrased her question and said if we could do it all again from the start, would we still get the LNT model. David Brenner said that it is reasonable to use the linear model and of course move to other things later.

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John Dunn came out and said that SARI isn't there to point fingers.

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Chris Clement said that he would like to talk about a few good things about the previous session. Appreciated a few points from Dr. Doss's presentation, we should be looking at the whole person. Unfortunately, we can look at people in cages. The result is the protection of the whole human. Furthermore, we need to look at the protection of all people, not just one age. The other comment is about where we agree, if you get big doses, you get cancer and there are problems. As the doses go down, the risk goes down, I think most people still agree with this. The way he looks at it, once you get down to some level, results are lost in the uncertainty. You can argue that this shows a threshold, you can argue that it shows LNT, so anyhow we don't really know. In addition there are a number of definitive studies that don't agree with some other definitive studies. This is the situation that we are in right now. It means that we need to do some more research. The ICRP needs to run a system to protect people and the thing is, how do we protect people with such uncertainties. Anyhow, we do have to ask how we will behave with this uncertainty.

3:59P

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The guy from yesterday who managed the Nevada Test Site (Dr. Church), today he would like to speak about a person experience. In the last half of the 70's, his government decided that the DNE and ??? would go out and have to clean up the Nevada site. He thought that Darrell gave a really good presentation this morning. He said that if the LNT was the driver for the expensive cleanup and unfortunately having people getting killed as a result. He said that if this was the LNTs doing, he hates it. He said that we cleaned up to the level at which it was difficult to even measure radiation from the soil. With low doses and low cleanup levels, we were transferring that risk over to real people. He published

a paper, "The unacknowledged transfer of risk" which detailed his thoughts on it. But ultimately, we ended up killing real people to move dirt around and maybe we didn't have to do that in the end.

4:04P

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He found that there was almost no risk in moving all this soil from point A to point B. Utilizing this extremely low level exposure by the EPA which sounds like it ultimately came from the LNT. When you transfer a sixth order risk to a fourth order risk to a second order risk to injury... there is something wrong with that picture. We need to start thinking about the impact on real people, because we had to bury real people. We weren't burying these mythological people experiencing population doses.

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David Brenner said that his point regarding the 1 mSv limit was well taken.

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He said that his point is that if you think that this whole thing doesn't have an impact on real people, he wants people to know that it really does have an impact.

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David Brenner said that he thinks that there probably isn't a single person in here that thinks that the 1 mSv limit per year is reasonable.

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A response to the radon data comment that Tony made. Mohan Doss said that there are plenty of case control studies that compare lung cancer rates to low radon levels and high radon levels. The thing is to compare the cancer risk to see if there is an increase. One more comment about the very low doses point. If you are trying to measure the effect from jumping two times two feet every day, on your normal health risk, it will be within the noise. If we are talking about radiation levels that are as low as 1 or 5 mSv, you are just measuring noise and it has no relevance to human health.

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David Brenner agreed that when you get down to those really low levels, you are just measuring noise.

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He thinks that we should just start measuring from 50-100 mSv and up from there.

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David said that what epidemiologists do is to measure as low as they can, that is their job.

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He said to not waste time doing studies measuring noise.

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David said that we need a mechanistic study.

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Another questioner wanted to speak on hormesis. It does have an effect but that it is not universal.

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Two questions for Jerry Cutler, one to expand a bit more on treatment of gangrene and of Alzheimer's disease. The second question was about how he transformed data from the atomic bomb data.

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Jerry said that he moved one point because upon reading about it, that person seemed to have issues that were consistent with a much larger dose and as a result was probably not recorded correctly. We also have the evidence of pre-1960's studies. They used to use radiation treatment for a number of reasons, but we haven't done so since then.

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Question from Grant, he is here to ask the audience. He would like to see a vote of hands to see who would want to raise the general population dose limit from 1 mSv to 5 mSv. \*There was what appeared to be a majority of hands raised in response to this question.\*

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Mark Miller chimed in, he said that there were 24 mill sites that were qualified for cleanup and we had 4 incidental deaths during the cleanup. He didn't want to say that the cleanup didn't need to happen, but spending 3B dollars to kill four people doesn't seem right.

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Comment, it seems like there is a lot of discussion of people disliking the LNT model, but he suspects that the issue is that people are going beyond ALARA principle, they have gone beyond what is reasonable.

4:26P

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We were all amazed by Dr. Church's comments, and what we should be considering is that regulation should exist to create a net benefit, because real people can die during these cleanup efforts. Let's never forget that people go to work in dangerous professions to get a paycheck. However, let's remember that those people were getting some benefit.

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Mr. Church responded saying that yes, these people did get paid and he doesn't have an issue with people doing risky jobs if there is a reason. However he doesn't view moving dirt around as a good reason. On to next questions

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Nick Daniak, says that he is detecting some movement here in this discussion. Tomorrow we will be wrapping up with a path forward. There is a lot of talent here in this room. He said that we really need each other Radiation Biologists and Epidemiologists to find a path forward that at least most people can move forward with.

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Chip Ribble, commented on the story about the workers at the Nevada site. In all fairness, that was in the 70's right, but the project manager of that thing should be responsible. He isn't OSHA either, but he takes a certain ownership of things. He has to see and if he sees, then he has to report issues if things are not being done safely. So anyhow, there is a way that this should be controlled. He does want to admit, that this sort of loss of life is probably not taken into consideration when calculating risk assessments. Anyhow, it is a very compelling issue.

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Now the final question.

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Article today is that Trump is planning to loosen the EPA radiation limits based on Calibri's papers. He had a thought experiment of what radiation level if high for a year would cause people to leave that night and relocate. It sounds like most people probably wouldn't relocate on account of a 100 mSv dose over a year.

4:36P

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Plenary Session #6 : Needs in Low Dose Radiation Biology for Medicine and Industry [Chair ; Michael O'Connor]

The keynote address for this session will be Cynthia McCollough, who will speak on "Benefits of the Low Doses of Radiation Delivered in Medical Imaging". She wants everybody to turn off their cellphone, not silence, turn off. Cellphones emit deadly radiation. Why do we have such exponential growth, because the benefit exceeds the risk. Individuals deem the benefit to be greater than the risk, thus ditching landlines for cellphones. If there is even the slightest risk, there will be people dying. Lets use ALARA for this, buy headsets with cables that are AS LONG AS REASONABLY POSSIBLE. This will be inconvenient, so lets go back to pay phones. However, there may be some other problems if EMTs cant reach people in distress.

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Now on to CT scans, their use is also growing exponentially. They are growing in use because the benefit outweighs the risk. If there is even the slightest chance of CT risk death, thousands of Americans may die. But all actions have consequences, think of your families medical care. If we take away CTs, we could put in MRs everywhere because they don't release ionizing radiation. Oh wait there is a problem, MRs take 60-90 minutes, versus the 5 minutes of a CT scan. However, there are some circumstances in which time is of the essence, and sometimes you need to figure out the result of trauma. There was a case of a child who fell from a tree, and did not get a CT scan in fear of exposing them to radiation. However, the child died a few hours later due to internal issues.

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So what is the risk of a CT scan. Some people out there did some math. They knew how much radiation comes from BIER VII, and they multiplied that against a population size. How to quantify the benefits of CTs. Medical experience can quantify this. Can find an issue with aortas quickly. In another case, there was a spinal issue. They did a CT of this person who had an abnormal spinal cord, there were going to perform a biopsy, but they decided to do a CT first... upon closer inspection it was an artery which carved that cavity through the spine. If they had done a biopsy it likely would have killed the patient.

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In a different study, they looked at whether an ultrasound should be performed before doing a CT scan. The paper was pretty biased against CT scans and. Other ways to assess benefit. Have clinician/surgeon determine a leading diagnosis before looking at CT scan results, then show them CT results. Next time see how often the doctor's changed their diagnosis following looking at the CT. The CT helped confirm or exclude 95% of alternative diagnoses. How to quantify the benefits of CT. Prospective, blinded, randomized trials. This is the gold standard. In 2010, NLST and NELSON lung screenings found statistically significant 20-26% reduction of lung cancer mortalities to people who received CT scans versus those who didn't.

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There are groups that put together guidelines. They like using this nice radiation symbol for radioactive tests. Due to the way they list the CT scans, it is highly unlikely that doctors would pick a CT.

Consequences of alarmist media messaging. She had an 84 y/o male who was going to have an abdominal aortic aneurysm. A pre-surgical CT was scheduled, but he called and wanted it canceled due to fear. So should we reduce CT dose or not. Yes, we should reduce the dose not because it will cause cancer, but because people fear it will cause cancer. Also, CT is so beneficial that it will be used more and more as time goes on. Now don't reduce the dosage too much. Unfortunately, if we go too low then we don't see enough and we might miss something that we need to see.

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So this is logical, so why isn't it working. This is because perception of risk is not logical. Closing thoughts, she appreciated Roger McClellan's talks, however medicine needs somebody else. We need somebody to weigh the demonstrated benefits over the unproven, small or potential non-existent risks and responsibly distill knowledge. Then we need some societally distilled messages. She would like this community to get the message out that medical imaging is safe and that the bar for ordering should be low. Yes it should be justified, and it should be optimized.

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Question, if you want to reduce the CT dose a little bit. How much do you need to pay to accomplish that.

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You can do economic dose reduction by basing the dose on the size of the person you are scanning. This technology is already coming along in new equipment.

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There was thanks and a question if her slides would be available.

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Cynthia said that she gave the slides to the conference so they should be available there.

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It was asked if there was no issue with that level of dose, then why are you trying to get that dose reduced even further.

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Cynthia said it is only being done because it would reduce fear from patients.

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Cynthia said that the health physics and the radiation experts need to say it more.

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Question: What we learned the CT scans over the past few decades is that CT scans are overwhelmingly beneficial. So much so, that there really isn't a reason to do a risk benefit analysis. He said that the issue is that there are a lot of CT scans that are ordered that didn't need to be ordered.

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Cynthia said that the issue is, when a CT scan is done and they don't find something, they would say that it was an unnecessary CT scan.

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Jim Conca will now speak on the value of a human life (What do inappropriate low dose standards cost). The problem as it stands, Radiation Risks to humans and the environment are assumed to exist as a result of any exposure, no matter how small. Exposure to natural background, is, on average about 3 mSv/yr although global region averages range between 0.3 to 100 mSv/yr. What are the costs of regulating doses down to such low levels and how much do we consider the value of a human life to be. If you are the EPA would you consider it to be \$7M. However \$316,000 is the average pay out in health care over a life. 129K is the average historic legal value, \$12,420 is the death benefit to deceased soldiers. Or \$45M if somebody is carved up and sold as parts on the black market. To protect the theoretical human lives from LNT , we spend 2.5B per theoretical life.

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However, if you spent \$100 instead on helping kids in Africa avoid disease, there would be a much bigger benefit. Our regulatory limits are so far down in the noise as to be meaningless from a public health standpoint. However, the LNT demands that there be an effect. With LNT you HAVE to see the effect. If something else were going on (i.e., a threshold), then LNT isn't correct. He would like to talk about some behavioral risks facing Americans over the past 5 years. The most common death (from a provided list) was iatrogenic (medicine gone wrong). Smoking was the second highest killer. Alcohol is still high up there. Accidental falls are pretty high up there. Considering the relative danger index, dying from food poisoning is still more probably than dying from a nuclear power related accident.

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What are some of the costs associated with exceptionally low radiation limits. Commercial Nuclear Industry increases costs and increase fear of nuclear Power. Environmental concerns, fear prevents the use of nuclear power from addressing climate change. Nuclear waste, increases cost of repositories and prevents siting at the most optimum and geologic locations. Medicine, causes radiation phobia which prevents patients from utilizing medical diagnoses. Causes extreme radiation phobia following nuclear or radiological incident and accidents. Loss of lives and severe injuries associated with frantic evacuations. Fukushima is one of the greatest examples of this. There was an evacuation of 160,000 people from provinces surrounding Fukushima which resulted in about 1,600 deaths, mainly of elderly and disabled. Most adults could have returned after 2 months.

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Over 50% of the residents have finally returned, mostly older citizens, but the damage has been done. Government estimates the cost at over \$200 US Billion. Japan's government foolishly lowered the radiation limits on food after Fukushima thinking that would appear as proactive. Unfortunately, as a result of lowering those radiation limits, they destroyed a lot of farms. The main effect has been to completely stop our nuclear waste disposal program because of fear, preventing science-based decisions. Gave us glass over grout for HLW, even though grout is better, and cheaper for most HLW. The Hanford vitrification program, not including repo costs is expected to go over 90B.

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The waste out at Hanford is bomb waste. There are two sorts of waste that remain, high level waste (metal waste), and trans-uranic waste. Since 1970, most Cs/Sr has been removed and others mostly decayed, so now tanks are for TRU. However, we haven't treated this as such because of LNT. The DOE did an environmental impact study on the Tanks. If you do nothing and walk away, the radiation dose is 4.37 mrem/year at the rivers edge. Can you really believe the three significant figures on this??? So you can spend \$250B extra to get that number down from 4 mrem/year to 1 mrem/year. Is this really a good use of \$250B. If you just grout the tanks in place, you drop from 4 to 0.9. However due to LNT, this isn't an option.

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If you raise the dose cleanup limit from 15 mrem/yr to 100, you save about 420B. On to questions.

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Why are you pinning the blame of so many things on LNT. The high level waste issue is more that the high level waste was not allowed to reclassify that high level waste due to legal issues.

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Right, I do agree that it is political. But you need to think about why this lawsuit was filed to disallow that reclassification. You need to think about what is driving those legal issues. It is really because the public is afraid.

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The fear of radiation is there, even if we change to a different model, The problem is that you have a population that has been raised to fear radiation. On to the next speaker Wade Allison, who will speak on "public support for nuclear energy". Wade said that he normally doesn't like overused stories. However, the elephant in the room is the public. Unfortunately, it will take many generations to get this right. We need to start telling people different things in schools, so that they can go home and tell their parents at home, and maybe then they will start to understand the situation.

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In prehistory, a clever ancestor brought fire into their home. The clever environmentalists of the day probably proclaimed them to be mad. When the confrontation happened, the green environmentalists went home with uncooked food, were cold and died. The people of the pro-fire party, went on to invent boats and survive. Much later in the industrial revolution, you have coal replacing bio-fuels, and steam replacing water and wind for transportation. The effect on nature, had not been fully understood. Most people in 2018, are now of the opinion that this may have been a mistake (climate change).

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Choosing a source of energy. The renewables have a very low energy density. These are good because they are familiar and accepted. As an example, England's green and peaceful land has turned blue with solar panels. If renewables are not going to do the job (they are intermittent). Excluding carbon sources (due to pollution), Nuclear is the only viable option. It is compact, safe, reliable, and has roughly no impact on nature. The primary disadvantage of Nuclear is that it is unfamiliar and feared. Unfortunately, the populace has been learning that Nuclear has been dangerous for 75 years. We have inept safety regulations in place, which are preventing us from moving on to non carbon emitting sources of energy. Nuclear is safer than fire.

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What should we tell those kids at school. Using multiple copies on two scales. 1 many individual organisms, 2 . Many cells within each organism. In both cases cyclic replacement. In both cases defense

by talking, hence 1. Cellular Bystander Effect, 2. Social Bystander Effect. the talking should be informed. Clearly the cells have by evolution have got their act together and the relationship between cells works together toward the survival of the organism as a whole.

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Defense against an oxidative attack. Required for survival over 3500 million year ago. Signal too small for individual scale. So protection devolved to cellular scale by repair/replacement/anti-ROS/adaptation/immune. Response is resource-limited, hence nonlinear like other resource-limited systems (e.g., in electronics, management, ...). Linearity would be unnatural in an evolved or designed system. Public: Show the evidence! It is like doing business at an office, if you have three phone lines, then you can handle a certain number of business at the same time, but beyond some point you start losing customers.

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The next question is; how are we going to tell and persuade the public that this is actually true. Ask the animals at Chernobyl, individuals unaware of radiation but with complete cellular protection, and now benefiting from the absence of humans. So what went wrong for the humans. An apology published back in 2002, chairman of ICRP admitted that the Swedish authorities enacted too strict limits on nuclear power. One problem with ionizing radiation is that the phrase itself evokes a sense of danger. They themselves were afraid to say that small doses of radiation are harmless, and their failure to connect with other people and the public, only prolonged the fear.

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Unfortunately none of these reports were sufficient to placate the public. Evidently the curse that damaged human lives came from regulations, not radiation. Wade did his best to inform the media of the actual harm resulting from radiation, but they decided to run with the story of fear instead. The radiation dose-rate safety threshold. To protect the public from harm, not the authorities from litigation. The ICRP recommendation for workers (1934): 60 mGy per month, we know enough for safety, Lauriston Taylor (1980). Same for all. Youth and pregnant mothers have the best immunity. Mother nature doesn't care if I get cancer, but pregnant mothers and children have the best immunity.

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On to conclusions, we should reinstate the threshold dose rate from 1934 (60 mGy per month) (ICRP 1934). Cease reference to accumulated dose as a significant risk factor in radiation protection. Cease the use of linearity and related risk coefficients. Educate, reassure and inform the public and authorities, including UN, that ionizing radiation at rates below threshold is not harmful and that no distinction is needed for children and pregnant mothers. Facilitate the use and construction of nuclear power plants to mitigate climate change and enable ongoing economic activity. Reduce the cost of nuclear technology by a large factor by ensuring that all safety provision is based on science. Construct fast nuclear powered shipping for cargo and passengers and reduce air transport.