MICHAEL SHORT: So as a quick review of all the different biological effects, we've pretty much taken it up to here. We've explained the physical and chemical stages of what happens when radiation interacts with mostly bags of water with some solutes in them, better known as organisms at dynamic equilibrium. Everything from the sort of femptosecond level, ionization of water almost certainly, because that's most of what biological things are, to the formation of many, many, many, many, many different radiolysis byproducts eventually that end up as just a few that we care about, the longer-lived radiolytic byproducts that will then diffuse away from the original damage cascades and go on to eat something else, likely DNA or something that you don't want to get oxidized or chemically changed.

We talked a little bit about radiolysis in reactors and how you can actually measure it directly which was only done really a few years ago which is pretty cool. Just to remind you of this experiment, there's a tiny high-pressure cell of high-pressure, high-temperature water. There is a foil sample with a very thin region and protons firing through it, so that they both irradiate the sample and induce radiolysis in the water at the same time. And this way, you can test the effect of radiolysis in the water here versus just plain, old, high-pressure, high-temperature corrosion here. And the results are pretty striking, where you can clearly see the boundary where the proton beam was as well as the increased thickness of the oxide and corrosion layer formed when radiolysis is turned on, so to speak.

We went through DNA damage, and we ended with pseudoscience. So I want to bring up a couple-- no, we don't have time for that. But we spent the last 15 minutes of class railing against pseudoscience and making sure that you check your facts, but we pointed out a number of things wrong with some of the studies. So aside from just that guy misreading everything on that entire blog, of the studies that you felt weren't very convincing, what do you remember about them? Some of those studies were totally fine, but some of them were not.

AUDIENCE: The ones with particularly small sample sizes.

MICHAEL SHORT: That's what I was hoping someone would say. Yeah, the case study of four women who got breast cancer in the pocket where they held their cell phones, four, right? Or in a study of 29 humans, 11 of them got brain tumors here. It's pretty easy to cherry pick small amounts of data.

I did want to say that just because radio frequency photons aren't ionizing, doesn't mean they can't hurt you. If you've ever-- no, no one's ever been inside a microwave. I wonder if anyone's ever felt the effects of an external microwave being by something like this, the active denial system. One of my favorite weapons ever, because it doesn't actually permanently hurt anyone. It just heats up the outer layer of your skin.

It fires these non-ionizing photons at RF frequency and effectively makes you feel like you're on fire. So if there's a whole mess of troops charging at you-- let's say at the DMZ from North and South Korea-- all you've got to do is turn on this thing, and they all think they're on fire, because their body is sending them signals that I'm on fire. And then you turn it off, and they're OK. So no loss of life, no permanent damage, a lot of maybe psychological, but whatever, you can't see that.

AUDIENCE: Active denial.

MICHAEL SHORT: Active denial system, great name for it, isn't it? Yeah, I think non-lethal weapons are really the way of the future is just make it unpleasant to engage in warfare, and people probably won't. But then no one has to get hurt, which is nice. But then onto the sources of data, because like Sarah said, sample size is everything, especially when you're trying to figure out, are small amounts of radiation bad for you? This simple question hasn't really been answered suitably yet, and that's because, thank god, we don't have enough people exposed to small but measurable amounts of radiation to draw meaningful conclusions from this data.

I think that's a good thing, is if we were certain about whether small amounts of radiation, like one millisieverts, could cause cancer, then there would have been millions or billions of people exposed, and so it's kind of a good thing that they weren't. But the sources of this data, the first source was radium dial workers, like you may have heard of, the folks that would lick the paint brushes with glow in the dark radium watches. They ended up setting the first occupational limit for dose, because they were the first large group to be exposed to radiation in a controlled setting.

Things like uranium miners, radon breathers, better known as us, but especially folks that

smoke anything. Medical diagnostics, so anyone that gets a medical procedure, you can follow up with them to find out what's, let's say, the extra incidence of cancer and figure out, if you have a high-dose medical procedure, does it induce secondary cancer down the line? But like we said last time, down the line is the key here. I'd take a whole bunch of radiation now, if it was going to save my life now, and maybe make it messed up in 20 years. Because then you get 20 more years of life or however long you get.

And then from accidents, survivors of the atomic bombs, not just the folks at the epicenter, but in the whole fallout regions and nearby, as well as nearby nuclear accidents and the criticality events like the demon core that you guys analyzed on the exam. Luckily, there aren't a lot of those, either. But they were pretty severe, the ones that got exposed.

And speaking of accidents, has anyone ever heard of the Kyshtym disaster? This is the third-worst nuclear accident that we know of in history, after Chernobyl and Fukushima, and worse than Three Mile Island, because Three Mile Island was an almost accident. There was some partial melting of the core. There was almost no release of radioactivity. And the definition of a nuclear accident in the public sense is release of radioactivity.

There's actually two quantities that folks in PRA, or Probabilistic Risk Analysis, are most interested in. Has anyone heard of these terms, CDF and LERF? Core Damage Frequency and Large Early Release Frequency. All the fancy probability fault trees and everything goes into calculating the probability that the core gets damaged. So that could be an accident in one right. Or the probability of a radioactivity release. And that is an accident.

So if no one's ever heard of this, there's a city in Russia-- I don't know why it says Russland, maybe came from a different language-- called Kyshtym, where they had the Mayak nuclear and reprocessing plant. And there was a tank full of radioactive waste that was exploded. It was a chemical explosion, but full of strontium, all sorts of other radionuclides that blew up with about 100 tons worth of TNT, and ended up contaminating a rather large area with this plume called the-- I think it's called the East Chelyabinsk Radioactive Trace-- or the-- what is it? The south-- South-something Urals Radioactive Trace.

And that area is still contaminated today, because the disaster was covered up, or rather wasn't-- nothing was said. These towns here, they didn't-- weren't actually towns back in 1957 when this happened. They were just given designations, like Chelyabinsk-40 or Chelyabinsk-65, because the largest nearby city was Chelyabinsk, and the villages nearby were just

numbered. So that was just the post code for the secret nuclear city.

The US had a few, Russia had something like 120. And they still have a lot of cities where entry is restricted, or it's still awfully difficult to go there. Like when you have to declare where in Russia are you going to get a visa, if you say one of these cities, there's going to be some questions. And this is where I'm going.

AUDIENCE: To one of those cities.

MICHAEL SHORT: Best possible logo for a conference being held in Siberia in February. Right on the end-- right on the edge in this town called Kyshtym, the nearest town to the Mayak plant. So I'll be taking my camera. I don't know if I'll be allowed to use it, but we're going to find out anyway. It's being held in a sanatorium. And does anyone know what a sanatorium is? Like, I'm honestly asking a question. I don't know what a sanatorium is or why the nuclear conference is being held there. But it should be pretty cool.

So yeah, Siberia in February, right near the South Urals Radioactive Trace, should be interesting. Those of the first group of folks that were exposed were the people painting radium watch dials. And the reason radium was so damaging is because radium is in the same column of the periodic table as calcium. It's a bone-seeking element. So which of the tissues do you think would be most damaged by ingestion of radium?

AUDIENCE: The bones.

MICHAEL SHORT: Bones-- what part of the bone, specifically?

AUDIENCE: The marrow.

MICHAEL SHORT: The marrow. The rapidly dividing part of the bones. If you remember from the-- I don't have it on this presentation, but the relative tissue factors for different tissues, the hard part of the bone is a 0.01. It's basically like a nobody cares. Bone marrow, however, is a different story, because it's always rapidly dividing, producing red blood cells, platelets, lymphocytes. It's making your blood, the solid portion of your blood. And so it's a pretty important tissue. So you get radium-- anyone also know, what does radium tend to emit? Which kind of particles?

AUDIENCE: Alphas.

MICHAEL SHORT: If you have to take a guess-- yeah, alphas. It's a pretty heavy element. It emits alphas. And

alphas have that radiation quality factor of 20, meaning alphas have very short range, but they're the most damaging type of radiation when ingested. So this was really bad news. There was a lot of incidents of illness and cancer from folks painting radium watch dials.

And then the first data from bones after death, because there were a lot of those, established, how much radium were you allowed to get exposed to? And this came out to about 0.6 milligray per week. Anyone have any idea what that would be in millisieverts per week? With a quality factor of 20 and a bone marrow factor of about 0.12?

AUDIENCE: 1.73?

MICHAEL SHORT: Yeah. On the order of like singles of millisieverts per week. Not bad. Anyone know how much dose you typically get in a year in background? Yeah?

AUDIENCE: A few.

MICHAEL SHORT: A few millisieverts a year. Yeah. So this was the first occupational safety limit for radiation risk. It is-- actually, it comes out to larger than 50 millisieverts per year, which is what the normal occupational workers are allowed. How about you radiation workers? What's your limit?

AUDIENCE: 5 rem.

MICHAEL SHORT: 5 rem, which comes out to?

AUDIENCE: Like 50 millisieverts--

MICHAEL SHORT: 50 millisieverts per year. OK, there you go. Large population sizes that do exist that get a whole lot of radiation, however, is anyone that smokes an anything, because when you take plant matter, which has a high surface area, concentrate it, so anything that it brings up from the roots in the soil, or that settles out on the leaves in the air gets concentrated in the dry fraction, and then gets burned and inhaled.

A lot of those heavy metals that are radon byproducts and such are fairly reactive. They'll stick around in your tissues and give you a whole lot of alpha dose. So when you have populations of people who have or haven't smoked, you actually can figure out the number of extra attributable deaths to things like indoor radon, depending on if you live in a smoky atmosphere or not.

And so to distinguish the types of biological effects that we're worried about, we can group

these into two. There's short-term effects, which manifest themselves in hours, days, or weeks. We'll call that immediate. And then there's long-term effects, which tend to manifest in shortest, years, and longest, decades.

So things like acute radiation sickness is due to rapid cell death of a few different kinds over time. And which kind depends on the route of exposure, the isotope, the type of radiation, and the total amount of dose to those tissues. And if you guys have all-- what are some of the symptoms of acute radiation sickness? Like, did anyone read what happened to the folks in the demon core?

AUDIENCE: That their hair fell out.

MICHAEL SHORT: Hair fell out. What else?

AUDIENCE: They vomit.

MICHAEL SHORT: Vomiting.

AUDIENCE: Diarrhea.

MICHAEL SHORT: Diarrhea. All the fun ones, yeah. Well, we'll explain why these sorts of things happen with acute radiation exposure. Now if you don't get that much radiation exposure, but you do get enough to mutate cells you have what's called delayed somatic effects, anything from cancer, to straight up mutations, to birth defects. Any sort of permanent and reproducible modification to a cell's DNA that can induce mutations.

So let's first talk about the short-term effects because they're a little easier to understand. And because the doses were much higher, you don't need as much of a population size in order to figure out, did this affect-- did this amount of dose have an effect? So for things up to a quarter of a gray, pretty much nothing happens. That's quite a toasty dose. For gammas, that would be like getting five times your occupational yearly limit instantaneously.

Yeah. This is not something you'd want to happen. But it's not going to cause any significant ill effects. Up to a gray, you'll start to see a few symptoms, like nausea and anorexia. They probably tend to go together. If you're feeling gastrointestinally horrible, you probably don't want to eat much. And you will see things like bone marrow damage, like we talked about with the radium workers. Fewer red and white blood cells, less platelets, also means easier to bleed.

So a lot of the effects of radiation damage are not primary, they're secondary. Just like most radiation damage to cells itself is not damage to the DNA, but it's radiolysis of the water nearby the DNA, and eventual chemical migration to cause damage to the DNA chemically. In this case, it's not like radiation takes out your platelets. Radiation takes out the cells that create the platelets, the bone marrow. Meaning that platelets, if they live about three weeks, you'll tend to see a drop in platelet count when your production system gets lower.

This should sound strikingly similar to series radioactive decay because the same equations can be used to model it. Let's say you have a normal, stable platelet count. Eh, I'm not going to get on the board. I told you guys we wouldn't get to derivey anymore. But you've got some source of platelets, which would be your bone marrow. And you've got some sink of platelets, which would be normal cell death. So let's say there's a half-life or a lifetime of platelets.

If you kill a little bit of the source, then you'll see the sink start to decay. But the source will start to grow back over time from cell division. And you'll see the level pop back up again. And you can model it with the same first-order linear ordinary differential equations. Same ODEs as series radioactive decay, you can use to guess how many platelets you should have in your body at any time following a certain dose.

1 to 3 grays is when things get bad from-- go to bed from worse pretty quick. Nausea, anorexia, and infection-- tell me, why do you think infection results from radiation damage? Yeah. Let's hear everything, yeah. Front to back, let's hear it.

AUDIENCE: I was saying the immune system is most likely compromised because of bone marrow being compromised.

MICHAEL SHORT: Yep. The immune system's compromised. What else?

AUDIENCE: You're--

AUDIENCE: [INAUDIBLE]

MICHAEL SHORT: Is everyone going to say the same thing? OK. I have another story. So I agree with you guys. But it also has to do with these platelets. Anytime anything happens to you ever, cells tend to die. You clap your hands, you probably kill a few cells. You bump into something, you probably kill a few cells. You swallow some metal shavings, you're going to kill a lot of cells. But your body has got mucous membranes, and all sorts of things, and platelets in order to repair that

damage.

All of a sudden, if your blood thins out, and can start leaking from different places, or it's a lot harder to repair like physical leaks in your body, bacteria can get in. So the normal amount of bacteria you're exposed to every day, which is enormous-- there's theorized to be something like 10 times as many bacteria cells in your body as human cells. They're all over the place. They're just a lot smaller. Well, they can get into places that they wouldn't normally get in.

So what would normally be a pinprick in a simple immune response, with a suppressed immune system and a lower platelet count, becomes a much more dangerous thing. You could undergo something called sepsis. That's basically blood turning to sewage because you get a massive blood infection. This is, again let's say, a secondary or even a tertiary effect, but very real.

Hematologic damage more severe-- hema refers to blood. That's basically saying the same thing. Recovery probable, though not assured. Why probable, and why not assured?

AUDIENCE: Everybody reacts differently.

MICHAEL SHORT: That's true. Everyone reacts differently. It also matters how much treatment you get. So if you get a crazy compromised immune system, we have hospitals, and sterile bubbles, and all sorts of things that you can be put in. But if you don't get to a hospital in time to reduce the onset of massive infection, that's what could happen.

Then you go higher 3 to 6 gray, everything as above, plus diarrhea, depilation, hair loss, temporary sterility. Think the temporary sterility one's obvious. Why do you think diarrhea and hair loss would occur?

AUDIENCE: Isn't it like the fact that your-- the cells of your like intestines-- then you can't like hold it in anymore because the damage.

MICHAEL SHORT: Yeah. Exactly. The most sensitive cells are the ones that are rapidly dividing to make villi and stem cells in your intestines. Hair follicles, gonads, anything that's dividing all the time, is going to feel the effects of radiation damage much more severely. And barring any mutation, which may take a long time to manifest, the wrong damage to DNA, and the cell just can't divide. So it dies. And if those cells die, then that means that you can't uptake nutrition. And your body just flushes everything out in diarrhea.

Fatalities will occur in the range of 3 and 1/2 gray without treatment. And this is what's called the typical LD50. Does anyone know what an LD50 is?

AUDIENCE: The lethal dose.

MICHAEL SHORT: The lethal dose for?

AUDIENCE: 50% of the population.

MICHAEL SHORT: Right. So about 50% of the people exposed to 3.5 gray will die. This doesn't take into account difference in treatment, difference in person, or everything, it's altogether. And I'll go into what an LD50 for different things is in a second. And then over 6 gray, you get immediate incapacitation. Hits the nervous system. You get so many cells leaking out that the chemical signals for your neurons, sodium, and potassium, and other ions. Well, if all your cells die and leak out, then all of a sudden you're flooded with the ions that are normally kept in a very careful equilibrium to signal.

So you can actually get sudden unconsciousness in a matter of seconds to minutes from doses over 10 gray. So you just-- you just go out like a light, like that, and may not recover. What's an LD50? It's the-- it's whenever an effect gets an onset by 50% of the population. And there are different something-something 50 doses, depending on, let's say, whether something's therapeutic, toxic, or lethal.

The example I like to give is selenium. Does anyone know anything about selenium in the diet? It's one of those trace minerals that you need to survive, but can also kill you. If you need to get, about on average, 5 micrograms of selenium in order to produce certain enzymes that keep things going in the body. 5 micrograms is not a lot. But you know that in order to have a little bit of selenium, it's got a therapeutic effect. Once you get around 5 micrograms, most people will see some sort of biological benefit.

If you get 5 milligrams, starts to become toxic. And this is the case with pretty much anything. Vitamins-- anyone ever had-- this is probably going to be a no-- anyone ever eaten raw seal liver before? Or polar bear livers? I don't know. No one's gone up, way, way up north?

AUDIENCE: Vitamin C.

MICHAEL SHORT: Anyone-- do you know why? Or--

AUDIENCE: Because they have too much vitamin A--

MICHAEL SHORT: Indeed. Vitamin A, something that you need a whole lot to survive. It's so concentrated in the livers the seals and polar bears that if you were to just eat a polar bear liver, you would die of vitamin A poisoning.

[INTERPOSING VOICES]

AUDIENCE: --you'd be dead.

MICHAEL SHORT: So I didn't hear all those things at once. One of the time.

AUDIENCE: If anyone ever offers you that, you just say no.

MICHAEL SHORT: Just take a little taste. You know, it's all about the amount, right? What were you guys saying?

AUDIENCE: If we had eaten it, wouldn't we have died?

MICHAEL SHORT: Well, no. It's not like you take a taste and you die. Again, it's all about the amount of exposure. One little taste is not going to flood your system with vitamin A. But you eat an entire polar bears liver, you're going to have a bad day.

AUDIENCE: Why does it have so much vitamin A?

MICHAEL SHORT: Wait, what?

AUDIENCE: Why does it have so much vitamin A?

MICHAEL SHORT: I don't know why polar bears have so much vitamin A. No idea, actually. But then beyond that, you can get lethal effects, where you might get sick from eating too much of something. But then again, you know-- anyone ever heard of the old hold your wee for a Wii contest? Where we found out really the LD50 of water?

Yeah. So you drink way too much water without any other solutes, you deplete your body from electrolytes. And then you can also die. So I ran into this experience personally. I don't have to ask any of you guys. I went hiking with my dad in Nepal, in 2009, and the last vacation I've taken-- that's a long time ago. It's kind of cool. At MIT, it's fun enough here that I haven't felt like I've needed a vacation in, what, like seven years? I'm actually kind of taking one this year because I'm going somewhere for research and just sticking around.

But we went hiking in Nepal I eat something I probably shouldn't. In fact, everyone eventually ate something they probably shouldn't. And I had what could be described as massive GI syndrome-- Delhi belly, whatever you wanted to call it. My brother likes to call it poop and mouth disease, because sanitation and stuff is not the best there. And so I was in a pretty bad state. And instead of drinking water to replenish all of the water that was leaving out of every direction from the body, drinking saltwater.

We took tablets that had the same isotonic concentration of electrolytes, amino acids, as those being lost by the body, because when water goes in the body, everything osmotically equilibrates. If you take in lots of pure water, it will-- a little bit of sodium, potassium, other electrolytes will dissolve into that water. If it's going out in any direction, it's going to leave your body, depleting you of electrolytes. So I had seven wonderful days lying in bed, drinking about a liter of warm salt water every 15 minutes or so in order to maintain not just the water, but the electrolytes that your body needed. Freaky, huh?

AUDIENCE: Sounds like a fun vacation.

MICHAEL SHORT: Yeah, it was a great vacation. Is there any wonder why I don't want to take another one? If I go back there, I'm having nothing but Clif bars. It's hard to say no when folks that live up in the mountains offer you what little food they have, but you should really say no for your own safety.

Anyway, yeah, there's an LD50 for water-- by any mechanism, from electrolyte depletion to-- there was a contest on the radio called hold your wee for a Wii. When the Nintendo Wii came out, they said, how much water could you drink without going to the bathroom? And someone's bladder exploded.

AUDIENCE: Like literally exploded?

MICHAEL SHORT: Yeah. That's what I heard. Either it would be a bladder explosion or an electrolyte depletion. So whatever the mechanism, the LD50 just tells if somebody-- if a population ingests a certain amount of something, or takes in a certain amount of radiation, how much will cause 50% to die. Or for much lower doses, 50% will see some therapeutic effect by any mechanism. It doesn't distinguish by mechanism.

So the four phases of radiation damage, this is where all those Latin and bio roots really come in handy. The prodromal phase is the initial symptoms of exposure, which may or may not

happen one to three days after exposure. For massive exposure, you're not going to see this, because you're not going to live one to three days. For very minor exposure, you may not even see these prodromal effects, like a drop in blood cell count, or GI syndrome, because the dose might not be severe enough for your body not to be able to cope with it.

The latent phase this, is the tricky one. An apparent recovery from the prodromal systems. So getting a medium dose of radiation-- let's call, that like 2 to 5 gray-- will cause some nausea, vomiting, and headache. And then you get better. And then you get worse in the manifest illness phase, because a lot of the things that radiation will do can be immediate. If you suddenly cause the body to release serotonin and induce the vomiting reflex, that goes away once that serotonin is consumed or dealt with. I don't know how the body would deal with it. And you might think you're getting better.

But the cells that divide rapidly have still incurred that damage. And you won't see that damage until they fail to divide in their normal amount of time. So things like GI syndrome and hair loss might not show up for a few days afterwards, because it's not like your hair will just instantly fall out, like there's some cell that is holding onto your hair follicle and then will just release it when irradiated. But those follicles won't continue to produce the keratin at the same rate, or in a different way, or I can't speak that intelligently about exactly the mechanism of hair loss, but it will take a little bit of time to get there.

And the final phase is a binary. Do you recover or do you die? Could take days, to months, to years to figure that out. And these weren't in the reading, but I wanted to pull some much better tables about what happens in each of these phases as a function of radiation dose. So when does vomiting onset? There are actually patterns to be seen here. So for mild, it may take a couple of hours after exposure. You may not stimulate the immediate release of the hormones that induce vomiting. But then as the dose gets more and more severe, could be anywhere from hours to less than 10 minutes.

So you can use the onset of things like vomiting, diarrhea, headache, loss of consciousness in severe cases, to gauge the amount of dose someone has absorbed in some unknown accident. Because it's not like if you're in some severe nuclear accident, and you don't happened to be wearing a very large range dosimeter, how do you know how much dose you've got? And how do you know how to treat the person?

Time can be your best weapon there, because except for very lethal doses, where you could

go unconscious in seconds or minutes, you've got some time-- hours to days-- to treat what happened. And if you can say, all right, I know the time of exposure, and I know the time of onset of headache, of diarrhea, of vomiting, you can figure out, roughly maybe within plus or minus a gray, how much dose you had and what to treat. There are probably smarter ways of doing this, but with nothing else, you've got time as a variable to help you figure this out.

Why do you guys think that your body temperature would go up upon exposure to huge amounts of radiation? What's with the fever? What is the fever a response to? Or could it be a response to?

AUDIENCE: Infection.

MICHAEL SHORT: Infection. So any sort of sudden massive infection would mount an immune response. And that would cause a fever because you've got all sorts of cells doing things, expending energy, trying to rid your body of the infection. What else? That's OK, something for you to read up on for the-- not for the-- for the practice homework. The one that I can't make due because it's after the last day of classes.

What about-- let's see-- headache, I don't think we've explained that well. We'll get into the diarrhea stuff. Let's go into the latent phase. What tends to happen? Well, looks like you get better, but blood work will tell you otherwise. And you can then tell how much dose you were exposed to after a certain amount of time by things like lymphocyte and granulocyte count, different immune system blood cells, also platelets, also all sorts of other things.

You can tell by a drop in certain blood cell levels how much dose you've had. And you can sustain a certain drop in platelets and immune cells without any ill effects. Something like 30% to 40% of your platelets could go away, you're not a hemophiliac, temporarily. You're still going to be OK. You can form blood clots in result-- what is it-- response to a nosebleed or a bruise, and these things aren't going to be life-threatening.

Diarrhea, for low doses, you don't really get any. So it looks like intestinal cells may be a little bit more robust than bone marrow. Except with really severe doses, you'll start to see that pop up once those cells fail to divide. Once, let's say, the existing villi die off, new ones don't replace them, and you lose your ability to uptake nutrition. And then depilation, hair loss. Beginning on day 15 or later, you might think you're out of the woods, and then all of a sudden, your hair starts to fall out. And that'll help tell you about how much dose you've had once again.

And then the critical phase, what happens when things go from bad, to better, to worse? How quickly does this happen? You tend to get things like infections, more severe infections, disorientation. On longer times, like seven days, your platelet count-- it's pretty proportional to dose. Same thing with the number of lymphocytes, lower, and lower, and lower. And then the onset time is smaller and smaller. And then you can see the lethality of these different doses, depending on the person, the treatments, the susceptibility, any sort of pre-existing conditions, which you might not know. Do you have a question?

AUDIENCE: Yeah. I was going to ask, for cancer patients, when you hear about them losing their hair, are they actually getting doses in like the 2 to 4 gray range?

MICHAEL SHORT: Cancer, yeah.

AUDIENCE: Because it's so concentrated.

MICHAEL SHORT: Radiation doses are pretty intense. So the dose to the tumor, for example, in proton therapy, which is the only one I've really read about, can be in the kilogray level. But the idea there is you fry the tumor, you kill it soon. Like you go beyond the lethal dose for those cells, while inducing much less damage in the rest of the surrounding person. And that's the nice quirk of protons, is you can do that in a very narrow range.

The straggle on 250 MeV proton beams is on the order of like, microns, less than millimeters, which is pretty cool. But a lot of the hair loss can come from the chemotherapy. Chemotherapy is better known as poison. It's just a poison that affects tumor cells slightly more strongly than the rest of your cells. But it is nasty stuff. And it's the chemo that can cause the hair loss as well. Yeah.

So would you attribute the hair loss to radiation or to chemo? I would say chances are it's chemo, depending on where the tumor is. I mean, if you have a localized proton beam coming in to treat a tumor there or there, you're not going to get much hair loss up here. But chemo penetrates throughout the whole body. As far as if you're getting X-ray therapy of a brain tumor, that I don't know. I really haven't looked into that. So good question.

And then the time and severity of these symptoms. Well, this is something I'd like you guys to read on your own, because it's tons of words on a screen. But it's something I suggest you read. It's not done that carefully in the reading, which is why I provided it here for you in the

slides.

And then going on to what these radiation symptoms mean, I wanted to translate a little bit of the Latin, Greek, whatever, roots into something you can understand. These hematopoietic symptoms-- anything to do with the blood, decreased platelets, immune suppression, all that kind of stuff. And the origin is the stem cell system in your bone marrow breaks down and you don't make as much of all the components of blood as you normally should.

The gastrointestinal comes from the stem cells in the villi, those high surface area structures in your intestines that absorb the nutrition, which are also normally covered in a thick layer of mucus to keep all the bacteria from getting out. Because nutrients, like, let's say, minerals or small proteins, are a hell of a lot smaller than bacteria, they can diffuse or transport through the mucus much faster. So you can uptake the nutrition and not let the bad stuff in.

And the neuro or cerebrovascular stuff is straight up blasting of endothelial cells. Your, let's say-- yeah-- I think that's skin cells. A term called edema, which is fluid leakage. Has anyone ever seen pictures of folks with massive edema in the legs? Like, folks that, let's say, haven't gotten out of bed for years and their legs swell up like this? That's just fluid leaking into the intracellular spaces. I'd say take a look. I don't think I'm going to show pictures of it because it's kind of nasty on the screen. But if you want to know what edema looks like, then I suggest you look it up. There's plenty of horrific stuff on Google Images.

And so what happens in these hematopoietic cells? About 1 gray can knock out about a third of your bone marrow cells, and that's actually OK, because those surviving cells are redividing quite quickly. And that means that you won't have that much of a drop in blood cells, because let's say you kill off a bunch of the bone marrow cells , but they redivide in a shorter lifetime than, let's say, the red blood cells or platelets live. You're not going to see that much of a dip in the blood cell levels, which are ultimately your main line of defense against sepsis.

Things like destruction of bone marrow, yeah that would-- that would be a bad thing. There's a whole lot of words here. I'd say this is better for you to read. I want to go through an explanation of some pictures of what tends to happen to, in this case, mouse bone marrow tissue after a lethal dose, 9.5 gray. That's what it looks like beforehand. That's what you're left with, is very, very few cells. So that would be definitely what a lethal dose looks like, because the ability to make all the things that bone marrow makes has been almost eliminated in this tissue. So a visual of what these sorts of things look like.

For the gastrointestinal systems-- I'm going to skip right ahead and show you what healthy and irradiated villi tend to look like. So I've been-- does anyone not know what I mean when I say villi? OK, good. So the little high surface area structures in your intestine that are normally great absorbers of nutrition, mostly due to their surface area, but also due to their structure and their biological function. And you tend to kill those off with a fair bit of radiation.

So this is what it looks like after four days, and seven days, and then 12 days. Things can recover. As long as you don't kill all the cells, they will divide and they will reconquer. And if the organism can live long enough to allow for that natural healing to take place, then you can survive an acute dose of radiation. So when we talk about why do you need hospital treatment, it's basically to stand in for your body's normal functions while your body regenerates those functions.

But for extremely severe cases-- let's go back to that table of how many, let's say, leukocytes, or what not you have-- or lymphocytes-- if you get down to the zero level, you've completely knocked out your body's ability to produce those. You might have a few cells left here or there. But at that point, there's not much anyone can do but make you comfortable. And then in this case, I think this was a human one-- yeah, OK.

So a healthy intestine from a human. It's got a rather small whatever that part is in the submucosa level. Lots of villi, lots of surface area. After radiation damage, when you have massive cell death, notice that the structures out here are pretty much gone. And there's a lot of scarring or-- what's the word that they use? Severe fibrosis. Why would your body make scar tissue in response to radiation damage?

So anytime your body senses that a whole lot of cells are dying, it's going to respond by attempting to repair. So like if you get, let's say, a small bit of surgery done, you could be left with some scar tissue. That's cells that have died, and when those cell contents leak out, they signal to the nearby cells, fix something. I can't speak any more intelligently about that, but the body does. And scar tissue is not what you want in your intestines because that interferes with-- what is it? Nutrition uptake as well as killing the structures that are doing that uptake to begin with.

Then there's the neurovascular stuff. Massive cell death from a huge amount of absorbed energy can just cause those cells to die and leak out, causing a lot of edema. That can cause a drop in blood pressure, which is also not good for you. This could be part of what leads to

some of the unconsciousness. If you have a drop in blood pressure due to any reason, then that can make you go unconscious. And there's pretty much not a prodromal or a latent phase. If you hit the neurovascular syndrome, you're pretty much going to go to the critical phase right away, within seconds, minutes, or small number of hours.

Here's another question, why the skin lesions? Because mature skin cells live about three weeks. If you kill off the skin cells in the dividing layer, and you don't reform new ones, and those skin cells die, you end up with the grossest word in this class, moist desquamation. It kind of sounds like what it is. That's like sloughing off of skin and leaving open sores because you don't have the ability to regenerate that skin, which is normally your first line of defense to everything, and you've got fluid leaking out. And it's just-- yeah-- it's moist desquamation.

Why the vomiting? Well, this question hasn't been fully answered yet. As far as back when I've looked at the literature around to 2011, there is a hypothesis that intestinal cells will secrete serotonin in certain conditions, including when they start dying, which would then stimulate a center in your medulla, the sort of automatic reflex center of the brain, to induce vomiting. Why might this be a good thing? We're not talking about radiation, but why would you want to stimulate this vomiting reflex?

AUDIENCE: In case whatever's going wrong is because of something you ate.

MICHAEL SHORT: Yeah. So let's say you eat a wet aged steak. You know, something that's left out on the table, or in the fridge, or let's say, behind the fridge, or left to marinate in the sun. And you eat it, and those bacteria start killing everything. If those cells in your intestine die, they've got to send some signal far away to the brain to tell you to get everything out of the stomach. And that's what happens. So the body has developed these long distance hormonal signaling mechanisms to say, something is going wrong, expel everything, because it's probably bad for you.

So radiation damage to these cells, which will kill them, may trigger the same effects. If those cells have little pockets or organelles that contain these hormones and cause instantaneous secretion by cell death, that might do the same thing, too. But as far as this paper, it's a hypothesis. It's not necessarily proven. But it does correlate inversely with the amount of time to vomiting, in terms of dose and time to vomiting. So that much we do know.

And then onto the long-term effects. There's two that are really important, is cancer risk and birth defect risk. You won't tend to see this happen, despite popular media. But you will see a

lot of bad stuff happen. These are extremely difficult to wrap our heads around. And the reason for that is the population size required in order to do a proper study with proper statistics, and give confidence to the saying, let's say, a dose-- in order to, let's say, a dose of 1 milligray would have some amount of excess risk, you'd need to expose 61.8 million people, plus a similarly sized control to distinguish whether or not 0.1 milligray has an additional amount of risk.

So let's say for gammas to whole body, what's 0.1 milligray in terms of increased risk dose in sieverts-- sorry-- 1 milligray? 1 millisievert. Tissue factor is 1, gamma radiation quality factor is 1, that's 1 millisievert. That's 20 years of exposure-- or 20 years of allowed exposure at the same time. Or 10 years of exposure at the same time, where 100 microsievert exposure at once has been said to say, maybe that's the onset of detectable amount of damage. Pretty difficult, and our sources of data for these doses are a lot smaller-- with the exception of very high irradiations than we need to make any real conclusions.

The largest sample size we have besides smokers would be atomic bomb survivors. So folks have followed all of the survivors of the Hiroshima and Nagasaki bombings. Not just the people nearby, but in the surrounding countryside. And tried to follow, how many excess cancers were there as a result of the radiation? For anyone exposed within 3 kilometers for less than 5 milligray, you can attribute, basically, either one or none. So by following this group of people and finding out how many of them got cancer compared to control groups, you can try and figure out, how much extra cancer was due to radiation?

And to graph this-- this is actually in the-- I think the ICRP publication, graphing the amount of relative risk, or to use the words from the last studies we saw, the Odds Ratio-- the OR-- of getting cancer, an odds ratio of 1 means exactly the same amount of risk with versus without the radiation. And the actual raw data points are plotted here. And there's a couple of lines drawn through here. And this is the source of a lot of the controversy behind radiation damaged nowadays.

The black line is the LNT, or the Linear No-Threshold model, which is a hypothesis that says every amount of radiation is bad, and it is linear with dose. I, for one, don't believe this model. This is, to me, a fear-based model. It's certainly easy to make policy based on this, because you can-- I think your average congressman can understand a linear graph. Not sure whether they could understand p-values and statistics. But they're-- they don't have to. It's what they ask scientists to testify about.

When you look at the actual data, there's this kind of funky shaped line along with plus or minus 1 sigma error bars. It doesn't really show a linear threshold, does it? It actually looks like it might be super linear for very small doses. And then it tails off, and then it picks up again. But this right here is a zoom-in of this data rich area of the graph. It actually looks like for really high doses, it might be a little super linear again, where things get much, much worse.

Hopefully you don't have anyone exposed to, let's say, 2 gray of dose, but the real controversy is here, in the small dose region. We don't really know enough to say whether very small doses are hurtful or not-- or harmful or not. In fact, they might even be helpful. So you guys, I think, were the first class that I-- no-- I had you last year-- no. You guys remember the answer to what is the idea that a little bit of radiation might be good for you? From the cash class? Anyone remember what that's called?

AUDIENCE: Hormesis?

MICHAEL SHORT: Hormesis, yeah. This idea that a little bit of something bad could actually be good for you. This is also a theory, and to my knowledge, has not been proven to be true. But it is evident in some other studies, along with different fields of research beyond radiation. For example, there had been an experiment where rats were kept in shielded lead boxes as opposed to just out on the bench where they got less radiation. And the rats that had less radiation had less incidence of cancer.

However, it's extremely difficult to remove all other confounding variables from this data. And that's the trick there, is when trying to tease out, are small amounts of radiation bad for you? You also have to tease out confounding variables or other things that might be obscuring your data.

Why the hormetic effect? So what are some of the ideas behind why hormesis might happen? So there are some theories, and some controlled studies showing that if you irradiate cells very lightly, they mount an immune response. There are proteins and things circulating throughout your cells that are there to repair DNA. And if you stimulate the production of those repair mechanisms, then the repair will be more rapid given the same amount of stimulus.

So in this case there are-- let's see-- I'm just going to say proteins-- I can't say anything more-- that will actually travel along DNA, looking for certain types of kinks or breaks and repair them. If those repairs happen before cell division, then the mutation is avoided. If you have more of

those repair mechanisms, it takes a little bit more energy to make them, but you also have less of a chance of a mutation manifesting itself past division number one. So this is kind at the cellular level idea why might hormesis be true, because you stimulate your body's ability to defend against this kind of stuff.

And so there you go. Cells can actually signal each other. So let's say a cell undergoes DNA damage and can't divide. These cells can actually send what they call kill signals in the intercelluar space to the nearby cells, stimulating them to mount some sort of response. Either release something or divide more to make up for the dead cells, which could be good or which could be bad. If you make more of these DNA repair mechanisms, that's probably a good thing. If you stimulate the nearby cells to divide faster, well what are the two things that could happen? Yeah?

AUDIENCE: More mutations.

MICHAEL SHORT: Why do you say more mutations?

AUDIENCE: Well, I mean, If you have cells that were in a radiation environment, that are exposed to that radiation you're dividing faster, each division has a certain chance of mutation. More divisions overall means more mutations [INAUDIBLE]

MICHAEL SHORT: Exactly, yeah. If there are cells nearby that have been exposed or mutated and you induce faster division, you may induce faster incidence of the-- what is it-- of manifestation of this mutation. But also, if-- let's say, a few cells die and the other ones divide to make up-- take up the slack, that might be a good thing. This is a normal way that you repair injury, is upon cell death, the cells nearby divide faster, fill in the gaps, and try and repair the tissue. So it's both a good thing and can be a bad thing, depending on what the nearby cells have been exposed to.

And so there's also this-- they call that the bystander effect, where, interestingly, you can have biological effects in cells that receive no radiation exposure if they're near cells that have received radiation exposure. There are some awesome experiments showing this. We had one here, back when we had a professor that did medical physics. She had created an accelerator with a microbeam, like a micron-wide proton beam, when you could irradiate single cells and watch what happens to the cells nearby. So to study in a controlled way, this bystander effect.

So if you irradiate one cell on a glass slide, how do the other ones respond? So you know which one was irradiated and you can watch what happens to the other ones-- pretty slick. That accelerator, actually, parts of that live on the DANTE proton accelerator that we now use for physics and things. But a lot of the parts from those machines are still here, just the microbeams and the cell parts aren't.

And then I highlighted a few of these passages in sort of the DNA damage bystander effect. One of the reasons is when cells nearby divide, they scale up their metabolism. They have to burn more energy in order to undergo division faster. And that can undergo what's called oxidative metabolism. Cells can produce energy aerobically or anaerobically. When you're dividing very quickly, all of a sudden, you start burning more oxygen to divide faster, to do whatever you have to do.

And that oxidative metabolism also creates free radicals just from normal wear and tear to your cells. And those oxidative byproducts may also induce mutations in the same primary way that radiation does. Radiation does hydrolysis, makes oxidative species that damage DNA. Chemical oxidative metabolism can produce the same sorts of things that can damage DNA in the same way, just a different initial effect. I'm going to stop here, even though we only have a few slides to go, because it's exactly five of.