Advanced Clinical Focus: Detoxification and Biotransformation
Transcript – Class 1 Part 2

0:00
Welcome back! We're going to get into the history of toxicology, who first discovered that there might be something out there causing problems to something in here, and what did he first observe? Let's get right into it.

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Paracelsus, born in 1493, and lived till 1591; had a pretty robust life. He was the father of toxicology and he was the first to attribute illness to something outside the body, to external factors, to something that is influencing internal physiology. He established concepts of acute and chronic toxicity, so immediate, high doses of a toxin causing a problem in the short-term, and also being exposed to something that's going to cause issues in the long-term. He was recorded as saying that 'All substances are poisons; there is none, which is not a poison. The right dose differentiates a poison from a remedy.' And we're going to see a few examples of these. It's not about what the toxin is, it's more about what the concentration of that toxin is, because a very, very, very small amount not going to create many problems. A really, really, really high dose might kill you.

1:20
Let's establish first a few definitions and some words that are used. Firstly, toxic; toxic means something capable of causing injury or death, especially by chemical means. We might also call it poisonous. So when something is toxic, it's going to harm our physiological system. Something that I often ask my students after I present this definition is, do they think sugar is toxic? Does sugar cause injury to the body when we consume? I'm talking about white refined sugar; something to think about. Next we have toxin; a toxic substance that is produced by a living organism, like plants, animals, fungi, or bacteria. So we often use toxic and toxicant interchangeably, not really knowing what the exact definition is. And I will probably refer to both interchangeably throughout the course. But as a technical definition, a toxin is only produced by living organism. So for example, on peanuts, there's often a mold that grows that will secrete a substance known as aflatoxin, which is actually carcinogenic. Around the world, they've actually tried to regulate how much of the aflatoxin ends up in peanut butter, because it is so ubiquitous with peanuts; so toxic. Toxicant is a type of poison that is made by humans or introduced into the environment by human activity. So you'll also see that some of these terms overlap as well. But a toxicant is something that we made; something synthetic that we introduced into the environment.

3:19
A xenobiotic is a chemical compound that is foreign to or not normally produced by the body. A lot of those chemicals that we saw with Sandra's case were xenobiotics; they're not recognized by the body. Xeno means different or foreign, and biotic means life, so foreign to life. Then we have something called persistent

organic pollutants, and these are substances that persist in the environment or bio accumulate through the food chain and pose a risk of adverse effects to human and environmental health. And just as the name suggests, these are persistent and take a long time to biodegrade, some tens, even hundreds of years to actually leave the environment. For example, DDT is a persistent organic pollutant. It was banned in the 70s, but we still find it in body tissue samples with people all over the world. So they persist, they're very hard to break down, the environment doesn't break them down easily, and they can bio accumulate because of this. Toxins build up the food chain; for instance, you have a little fish, and a big fish comes and eats a lot of those little fish, and a bigger fish comes and eats a lot of those fish, and because there are more and more toxins these animals are being exposed to, which accumulate, we have what's called bioaccumulation, an increase of toxins as we move up the food chain.

4:53
Some words you might see when referring to liver detoxification. So I've got a picture here of the PubMed homepage, which is a wonderful website to find most research articles pubmed.gov. And they use all sorts of words to refer to liver detoxification, something you might want to be aware of. They use hepatic, which just refers to the liver. Detoxification, which refers to the way we get rid of these chemicals in the body. Biotransformation, which is also one of the words used in the title of this course, and that really just means taking one substance and converting it into another substance, usually a harmful substance into a less harmful substance, so the body can get rid of it. And metabolomics, which might be a little bit foreign to you, is the study of chemical processes, involving metabolites. So the byproducts of just regular metabolism and how that's going to affect our body. For example, we need to make estrogen, we make estrogen, it does its job, and then we have to detoxify it, and there are actually metabolites, there are end products from breaking down that estrogen that might have an effect on our body if not properly eliminated.

4:53
Now in toxicology, a couple definitions here, it's the study of poisons or the adverse effects of chemical and physical agents on living organisms. So we're talking about the study of how these chemicals affect the body and, of course, we're going into more detail on how to get these things out as well. Historically, toxicology has been concerned with the amount of poisonous substance that would be fatal. So this is sometimes referred to as LD50, which means lethal dose 50. So essentially, what they would do is they would take lab mice or rats, they would give them a dose and then they would increase that dose more and more until about 50% of that population died. That's called lethal dose 50 and then they apply it to human dosages as well. Obviously, they're not using humans as the subjects to figure that out, but they don't refer to subtle or long-term effects. If something might be subclinical, and not really killing someone, but mainly just affecting their health, toxicology hasn't really taken that into account. So you go to the doctor, and you maybe don't feel so well, they do a toxin screen on you and check your blood, but you have nothing out of their range. They're going to

say there are no toxins in your body. But you know that maybe you're exposed to something, it's working on a lower level and inhibiting optimal health, inhibiting you from staying at the top of this level of health and moving that way. It doesn't take into account the long-term effects. What if you're exposed to a specific toxin, and it's in your body for a long period of time? Usually when they're testing these animals, they're doing it over a much shorter period of time to see when that dose actually is going to kill about half of them. So as you can see, the study of medical toxicology might not be completely applicable 100% to optimal health, to someone who's trying to stay healthy, and to stay one step out of the toxin.

7:56
There are a few other ways we can look at toxicology and the lethal dose 50, and this chart actually helps to put it into context for us. As I go through this, I'm going to use iron as an example. We all know that iron is an essential nutrient. And in this first blue curve, on the y-axis, we have the percentage of individuals responding to this dose, and in the x-axis, we have the actual dose. So with the first blue curve, we have what's called ED50. And that's the median effective dose. Say we're looking at iron; where's the dose that about 50% of the people get the desired response with a specific dose? So at the bottom there, it's not going to do much, we get to the effective dose for about 50%, and then as we start to get our therapeutic effect. Then for a lot more of the population, as we increase the dose, we don't quite get to toxic levels yet, but we need higher dosages to get that. I hope that makes sense.

10:29
Moving on to the green curve, now, as we get to the higher dose of the therapeutic effect, we now start touching a possible toxic effect. So the dose required to get 50% of the population reporting a specific toxic effect. And you can see again, in the middle, you get about 50% reporting that. Now, as we're at the bottom of the toxic effect, and we go all the way to the top, we start touching the lethal effect. So very sensitive individuals will be right at the bottom there. They might be exposed to, first, a toxic level of iron, and now a lethal level of iron, and that's going to about halfway, do a lethal dose for about 50% of the population, and then, of course, all the way to the end with higher dosages. So you can see here, how as we move along the continuum, something that might be essential might actually end up being lethal. For example, with our iron, we all need iron, we don't want to be too deficient, and we don't want to be below that blue line. We want to be in the optimal range, which might be in the middle of that blue line. We probably don't want to be in the toxic range or close to toxic, which would be the end of that blue line. But as we go from the therapeutic effect, where we have the right amount of iron, then we can get into a level where we actually become toxic. Now, it's not going to kill us yet, but it's definitely not going to promote optimal health because we've got levels that are too high. And then we move into what's called the lethal effect, so it's going to actually start killing people. At first, if it's 100 people, it might be one out of 100, but then about halfway, we get to about 50 out of 100 and that's the LD50. So that helps to put it into perspective a little bit more and even to sort of understand

this concept in more detail. This just goes to show how some things that may not be harmful at all, most of the time, could be harmful as long as we manipulate the dosage. For example, water, if I just sit here, take six litres of water and chug it back, that can actually be lethal. Completely dilutes my electrolytes and that becomes a really big problem. I can't get rid of it fast enough. I actually heard on the radio a while ago, there was a contest to see how much water certain individuals can drink in a given time. And the winner got like a video game PlayStation or something; I forget what it was for. One of the individuals actually died during this contest and it was just from drinking too much water. Then we have caffeine, and you'd be hard pressed to get 118 cups of coffee in you, but in 118 cups of coffee, you've got enough caffeine to basically be equivalent to a lethal dose. Then we have alcohol and we know that alcohol can kill. It takes about 13 shots of pure alcohol or about typical 40% alcohol content to basically kill someone. Of course, alcohol, again, is a poison to the body; it has ethanol in it and that is toxic to basically all of our cells. We know that very small amounts of it may be a glass of wine a day; it has some other nice things in it like resveratrol that might be beneficial, and maybe very small amount of alcohol. It has a blood thinning effect and helps in that way. But as we get into higher and higher dosages it becomes toxic pretty quickly and then at 13 shots, it becomes a lethal. so just a little perspective there.

14:33
Now a few more principles on toxicology are firstly, hazard identification. We're going to use a cigarette here is an example; it's always a good one when describing an agent as having toxic potential. So do cigarettes have toxic potential? Yes, we've identified a hazard and usually you get a nice little sign on a bottle or on a cleaning product showing that something's hazardous. Then we have something called dose response, and this is identifying the concentration above which an environmental agent induces toxic effects. So at what specific level is something going to become toxic. They've typically used a measure called NOEL, which stands for no observable effect level, and we're going to talk about this in a bit more detail in a moment. Then we have exposure assessment, so the evaluation of concentrations in a relevant medium. For example, in this cigarette, we know that one cigarette won't kill you, but as we increase the dose, we have a higher dose response, and when we put it in a cigarette form, the nicotine is actually highly diluted. So you might be interested to know that one drop of nicotine is a lethal dose. But the amount in one cigarette is so, so, so small, that we need to be smoking those cigarettes year after year for a long time in order to build up that nicotine, or build up those carcinogenic toxins in there for it to actually become lethal. Sometimes the concentration might not be that high, but there still might be a toxin in there.

16:31
Let's hone in a little bit on NOEL, and this is the NOEL based risk assessment for synthetic chemicals, for chemicals that are manmade, made in a test tube, made in the laboratory. Of course, NOEL stands for no observable effect level. We'll see a graph on this in a moment. It's typically based on short-term observations. So

again, they're testing a lot of these synthetic chemicals short term, not looking over years, 5, 10, 15, 20 30, 60 years. Remember, a lot of these chemicals came into existence starting in the 1940's, so what are the effects on people who are 6070 years old today? It assumes a linear dose effect. So as dose increases, harm increases. But as we saw, at the beginning of that first class, there was an exponential increase in celiac disease with the introduction of glyphosate, so a lot of these chemicals can cause an exponential problem, as we increase them in the environment. It assumes individuals are biochemically similar. So it's assuming that all of us process toxins the same way, which I mentioned earlier, is not true. We can have an 8000-fold difference in how much we detoxify in the liver and it ignores windows of vulnerability. So what do I mean by that? Well, children growing are in a window of vulnerability. A specific toxin is going to affect a child a lot more than an adult, because their bodies are smaller, they have a lot more to process, they have a lot more to deal with in the environment, and they have much smaller organs and tissues. In addition, children's skin, for example, is about four times more absorbable than adult skin. So if we put the same sunblock on a child, as we do on an adult, they're going to absorb four times more into the bloodstream. So that would be a window of vulnerability. The elderly also are in a window of vulnerability and toxins are going to affect them more. If someone has a crisis, like a traumatic injury, or they're in a car accident or a surgery, they're in a window of vulnerability. And NOEL doesn't take this into account. It discounts potential cumulative effects of a low dose.

19:13
So, as I mentioned before, a lot of companies say it's in such a low dose, it doesn't cause any harm. So there could be a cumulative effect of these dosages and in fact, lead for example, is a perfect example because a lot of lead can be stored in the bone. Especially with women who might be accumulating lead through a lifetime, and then they get to menopause; as their estrogen levels go down, their bone degrades a little bit quicker, and it can actually release more and more of that lead into the bloodstream. So it doesn't take into account this cumulative possibility. It discounts toxin synergy, and I talked about toxin synergy with you a bit earlier, that one plus one plus one doesn't equal three, but one plus one plus one can equal six to nine; it can be many times stronger than the individual toxins on their own, and it fails to account for trans generational effects. So we now know that the genes of a fetus could be affected through chemicals from the mother. What's interesting is that in a female, all of her eggs are created by the third trimester when they're a fetus. Basically, the daughter, if that's a girl fetus, half of them has already been created while that fetus is still in the mother, so you've got the influence of three generations there; epigenetic effects across generations. How is that chemical going to affect the gene and then has that gene going to be passed on to the next generation? This is not taken into account.

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So NOEL based risk assessment for synthetic chemicals, if we see it on a chart, we can see that on the x axis, we are basically just seeing an increase in the dosage, and on the y access, we're seeing a severity of the response. And NOEL

is right when we start to see a response. We talked about some of the downfalls of the NOEL based risk assessment. We talked about some definitions, we looked at a bit of the history, and now we can understand a little bit about how, when we're talking about toxicology, it's not cut and dry. It's not black and white. There's a lot of gray area and we need to appreciate that that gray area exists as we progress through this course.