Rob Carter, Angelica Means, Justin Nguyen

Injustice of Agent Orange Podcast Script

INTRO

Rob: What is poison? Is it a chemical? When is its use considered a weapon? Is its intention important? Once it's been used, how long does it last?

Angelica: These questions are the silent cries of an unspoken controversy, steeped in uncertainty. They are infused into the very ground under the feet of an ordinary woman as she walks through the streets of Bien Hoa City, Vietnam. She's 22 weeks pregnant, heading to the local clinic to have another ultrasound scan, her third so far. She's a little apprehensive, but confident. Her first two scans showed that her child has no birth defects, but it doesn't hurt to have peace of mind. Or at least, that's what her friends, coworkers, and family have said over and over again. "You can't be too careful."

Justin: A word is on the tip of her tongue as she walks: orange. What was it again? A poison?

Rob: In the eyes of the U.S., it was just an herbicide, known simply as Agent Orange, the primary chemical defoliant deployed by the U.S. during the Vietnam War under Operation Ranch Hand ("The Dark Shadow of Agent Orange"). Beginning in 1962, the U.S. sprayed 73 million liters of herbicide to decimate the Vietnamese jungle and farmland to deprive Vietnamese guerilla soldiers of cover and food. Agent Orange constituted 62% of the total amount of herbicide sprayed (Martini 2).

Angelica: However, Agent Orange quickly became infamous, not just for its potency against plants, but for the cost it incurred in unsuspecting humans. First were reports of birth defects from Vietnam, later corroborated by a U.S. study on Agent Orange-induced birth defects on laboratory animals, leading to the discontinuation of the chemical in 1970 (Martini 100-101). But the damage was done, manifesting in both the environment and people.

ENVIRONMENTAL SCIENCE

Justin: Vague memories of this history arise in the mind of the Vietnamese woman. The war seems distant to her, but the relics of that conflict permeate the city she's always known as home: Bien Hoa City.

Rob: She's almost at the clinic now, but notices a thick fog obscuring the small wire fence and warning signs that mark the boundaries of one of the city's hallmarks, the dilapidated Bien Hoa air base.

Angelica: This former U.S. air base is notorious, as its soldiers not only sprayed Agent Orange around its perimeter during the Vietnam War, but also stored 98,000 barrels of Agent Orange, with at least four documented spills of the herbicide between December 1969 and March 1970 alone. What remains is severe environmental contamination from Agent Orange's toxic impurity, dioxin, specifically in its most toxic form: 2, 3, 7, 8 - Tetrachlorodibenzodioxin, also known as TCDD (Olson 2019).

Justin: In 1999, over a million parts per trillion of dioxin were measured in the soil of the airbase (Olson 2019). As recently as 2015, dangerous dioxin levels above GVN Allowable Dioxin Standards were measured in soil up to 390 cm beneath the surface in the ZI Area, one of the most contaminated areas of Bien Hoa Airbase. Similarly dangerous dioxin levels were measured in soil up to 150 cm below the surface in the base's Southwest Area, which directly borders residential areas (USAID 2016). An estimated 340,000 to 415,000 cubic meters of soil needs to be cleaned (Olson 2019).

Rob: Unfortunately, this contamination is not confined to the airbase, as dioxins such as TCDD have a high affinity for biological compounds. So, they become concentrated in organic systems, especially in the food chain, through a process known as *biomagnification* (Olson 2019). TCDD binds especially well to fat tissues (Joffin et al.), especially in the fish populating the water systems in Bien Hoa, with dioxin concentration in fish measured to be "100,000 times higher than the surrounding environment" (Tuyet-Hanh et al.).

Justin: When considering that 81% of Bien Hoa residents living closest to the airbase in the city's Trung Dung and Tan Phong wards consume locally sourced freshwater fish on a weekly basis, the risk of exposure remains problematic (Tuyen-Hanh et al.). Although fishing bans have been enacted for the lakes surrounding the airbase, they fail to actively prevent contaminated food like fish from entering the diets of Bien Hoa's residents (Olson 2019).

MEDICINE & EPIGENETICS

Rob: This remaining environmental contamination by TCDD is a huge risk because of the many potential health effects and birth defects that exposure can cause. It's all the Vietnamese woman can think about as she arrives at the hospital for her ultrasound appointment.

Angelica: She scans the small, cramped waiting room–the other women there are around her age and likely waiting for the same scan. Her mind is flooded with images of babies born in suffering, a future she worried would affect her baby. She remembered the stories of waves of children born with disabilities, birth defects, or diseases, in areas Agent Orange was sprayed. But she had never considered that *she* or her baby might be affected. If she had never been exposed to Agent Orange when it was sprayed, how was this possible?

Justin: Unfortunately, her concerns are far from unique for women living in Vietnam today. While Agent Orange hasn't been sprayed in Vietnam for about 50 years, Vietnamese officials and doctors reported increasing rates of infants born with disability or disease associated with TCDD exposure *as of 2017,* mostly in areas surrounding Agent Orange hotspots (Sim 2019). And even if her child is born healthy, they could be severely affected later in life, as the population of 2 million in Vietnam suffering from cancer or other illnesses attributed to Agent Orange continues to grow (Vafeiadi et. al. 2013).

Rob: But if she hasn't been exposed during her lifetime or pregnancy, how is her baby possibly at risk of being affected by the chemical?

Justin: Scientists have actually identified two possible ways that the effects of TCDD can propagate in recent generations, by mechanisms that are either undetectable or have not been properly addressed in Vietnam in the half-decade since the war was over. The last two decades of research have found evidence suggesting that both continued direct exposure in the environment *and* the inheritance of changes in gene expression *without direct exposure* could be responsible for this. (Viluksela et. al. 3, 2019).

Rob: Because TCDD accumulates in the food chain and remains in soils & water sources, many people in Vietnam likely still come into contact with it through their diet & environment (Ngo et. al. 2006). The level of exposure individuals experience widely varies, but those subject to high exposure levels are at significantly higher risk. Reviews of data collected, since Operation Ranch Hand, show the risk of suffering from cancer or diseases associated with Agent Orange increased with amount of time of exposure, and the concentration of dioxin in the body (Ngo et. al 2006, Guri et. al 2004). The same pattern was found for the risk of sprayed individuals having children with birth defects. This suggests there's a **dose-response** relationship between Agent Orange exposure and health outcome: the risk one is affected is determined by the level they come into contact with.

Angelica: This means there is less risk for those exposed to extremely low doses, but the remaining TCDD in the environment can still meet toxic exposure levels. Dioxins are an infamously lethal chemical, and TCDD is one of the most toxic forms (Martin 2020). Even before its use in Vietnam there was knowledge of its toxicity. In 1988 an Air Force researcher associated with Operation Ranch Hand reported:

Justin: "When we initiated the herbicide program in the 1960s, we were aware of the potential for damage due to dioxin contamination in the herbicide. However, because the material was to be used on the enemy, none of us were overly concerned" (SBS Dateline 2019)**.**

Angelica: American forces knew the herbicide was dangerous to human health, but didn't consider how severely, until they found that U.S. Veterans who barely handled Agent Orange were suffering from the same diseases and various cancers as Vietnamese citizens sprayed directly. The chemical turned out to be lethal when one was exposed to very low concentrations, even low doses remaining in the environment can bring serious risk (Veterans Update 2019).

(STOP: Part 2)

Rob: If exposure to TCDD still in the environment is what's causing the continued suffering of Vietnamese citizens and infants, why hasn't there been a better job of cleaning this stuff from the environment, and why isn't there more progress in trying to prevent these issues? This information isn't clearly communicated anywhere that's publicly accessible--it took patching resources together that are only available with institutional access to find this out--why isn't the science more clear?

Justin: Unfortunately, the global and public health response to the Agent Orange crisis hasn't been significant because researchers cannot prove that Agent Orange directly causes the health impacts observed. We can only *speculate* on TCDD's causation, which is why diseases are only 'associated' with Agent Orange. Since the Vietnam War, the U.S. government has reported 14 associated diseases, that are up to four times more common in those exposed than in those that were not. (Veterans and Agent Orange 2019). But even though these relationships seem clear, there's been errors in tracking exposure since the war that makes data inconsistent, and there is no way to actually identify if someone born after Agent Orange was sprayed is exposed, so its effects can't be directly tracked in humans (Viluksela et. al 2).

Rob: The inability to prove children are affected also stalls the recognition of Agent Orange's impact on children: only 2 birth defects--spina bifida and neural tube defects--are recognized to be associated with the toxicant by U.S. officials, despite the prevalence of other defects including missing or malformed limbs, and impaired organ function, which affects the children of 13% of *Vietnamese* Veterans' sprayed, and 10% who were not sprayed or unsure (Children of Agent Orange, 2019).

Angelica: Despite suggestive dose-response evidence from dioxin hot-spot exposure, unlike American Vietnam War veterans, Vietnamese people remain unacknowledged by the U.S. in institutional classifications of Agent Orange health effects, despite their higher risk of exposure. Without clear evidence that TCDD causes the effects seen in humans, or even a standard of evidence, the U.S. is free to make decisions about who gets compensated and for which health outcomes.

Justin: What would be necessary for this accountability towards Vietnamese people?

Angelica: Proof, but the problem is that *proving* TCDD-induced negative health outcomes in humans would require exposing human subjects to the dioxin, so the best we can do is study TCDD in animal models and draw associations--no matter how apparent they may seem.

Justin: What if we focused on what occurs at the cellular level when someone's exposed to TCDD? Isn't it easier to observe how the effects we see occur at that scale?

Rob: Even when scientists try to look at cellular changes, we're still unable to fully understand how the responses to TCDD work, and at that scale it becomes more complicated. The rates of children born with birth defects in Vietnam has only dropped slightly in recent generations (King 2017), and persists in families who haven't been suspected to be exposed to Agent Orange in over 3 generations, which suggests Agent Orange mediates 'epigenetic' effects, that can be passed down to children who haven't been exposed.

(STOP)

Rob: We have Dr. Matteo Pellegrini, a Professor at UCLA, on the line right now. He directs a lab that is focused in epigenetic research, so maybe he can explain what this means. Hi there Dr. Pellegrini, can you walk us through what 'epigenetics' refers to?

[Dr. Pellegrini Interview excerpt]
Pellegrini: Epigenetics defines essentially the state of cells. [5.3s] Right. So all the cells in an individual have the same genome, but they have different phenotypic manifestations, different types of cells, neurons, blood cells, et cetera. The reason those cells are different, despite the fact that they have the same genome, is because they have different epigenomes. So, basically, the differences between the cells are what we loosely refer to as the epigenome. And they manifest themselves in different levels. Some are direct modifications of the DNA itself, like the example I gave you methyl cytosine. Some are modifications of the proteins that the DNA is wrapped around, so the nucleosomes--the DNA is not kind of free-floating in a cell. It's tightly wound all along proteins. And this affects, you know, the physical-chemical properties of the DNA. And so those proteins are bound. And how there are different from cell to cell defines the epigenome. [58.6s]

[00:16:53] And then you could go beyond that and say, you know, the current state of the cell, like, you know, which genes are being transcribed, how much they are. And so that could also be, in a sense, related to the epigenome. [8.9s] So sort of the downstream. But typically when we

talk about epigenetics, we're mostly referring to the first two. So, the direct modification of DNA and modifications to the proteins that the DNA is directly contacting.

Justin: Hi Dr. Pellegrini--we were just discussing how the effects of exposure to the toxicant, TCDD, persisted in generations who *aren't* exposed, suggesting it affects the epigenome. How do scientists arrive at this theory?

Professor Pellegrini [00:13:30] Well, I mean, you can know, you can tell whether they're easy to assay for a genetic change, by sequencing the individuals.

Rob [00:13:45] So as long as you establish it is not genetic, that's enough to say that it's epigenetic?

Professor Pellegrini [00:13:45] Right. I mean, there's only two. You know, obviously a genetic effect would be harder, because you'd have to have a compound that's mutagen. And so, it mutagenizes DNA, and that typically leads to cancer. So, you might know, people are exposed to radiation or, you know, like Chernobyl or something that should show up as some kind of, you know, higher cancer rates that could potentially persist for long times. But, you know, if you're seeing specific defects that are more endocrine tumors and then maybe that goes against the genetic alteration, and then maybe there's some kind of compounds that for some reason keep disrupting these and different mechanisms across multiple generations.

(STOP: Part 3)

Angelica: And we do have evidence suggesting TCDD is not a mutagen -- and extremely convincing evidence the toxicant impacts victims' epigenomes. In 1976, a factory explosion in Seveso, Italy exposed workers and nearby civilians to TCDD. The subsequent women's health study tracked exposed women and their descendants until 2010 (Emilia et. al 2014). Researchers found that TCDD is an endocrine-disrupting chemical, as it caused disruptions in steroid production, reproduction, and growth & development, even in generations born decades after the explosion. These chemicals interfere with hormonal systems, altering cellular responses to environmental pressures, causing cancers, birth defects, and developmental issues (Patrizi 1) .

Rob: Animal models later validated that TCDD is an endocrine-disrupting chemical, also meaning that it impacts the human epigenome. This means if the Vietnamese woman's father was exposed to Agent Orange during the war, he could have transferred the changes in his epigenome to the next generation: her. And these effects are proposed to be transgenerational, which means they can persist even in unexposed generations, putting her baby at risk (Viluksela 4). But the difficulty of proving this seems frustrating. We talked to Dr. Patrick Allard to obtain some insight.

Allard: [00:37:46] "So my name is Patrick Allard. I'm an associate professor in the Institute for Society and Genetics and I'm both a geneticist and a toxicologist.

Justin: Why is there so much uncertainty when it comes to studies about transgenerational effects?"

Allard: "[00:04:14] … if this indeed is transgenerational. Is there something molecular that we can look for? It would allow us to say yes that birth defect shows that molecular signature of an exposure to Agent Orange. And the problem is we're not there yet. And I think that's ultimately where the controversy comes from, is that in animal models, we can get causation, in humans, we most of the time cannot, right. We can have very strong suspicions, very strong indications. But getting to the true causation is difficult. So you switch to animal models and you try to get there. But when we do this, we have the animal model work and we don't necessarily know what to look for at the molecular level in people. That would be that difficult. So I don't necessarily have a good answer for you, except for saying that what you're describing is an issue within the context of Agent Orange is a very common issue in the field of epigenetics in general, and transgenerational inheritance, which is the fact that we have all these correlations and we have very little understanding of how it works. And therefore, we don't know whether these correlations mean causation or whether they don't, even in animal models."

(STOP: Part 4)

Justin: Even though scientists are limited, we do have a strong idea of how TCDD affects human epigenomes. We know it has a high receptor-binding affinity, and a half-life between 7 and 12 years in humans, so in those exposed there's a large window that it can alter cellular activity (Birnbaum 1994, Patrizi 6). Animal models have shown during this time, the compound binds to the Aryl Hydrocarbon receptor--also known as AhR, an enzyme that regulates transcription and cell growth, differentiation, and migration (Patrizi 2). TCDD binds the AhR forming a 'TCDD/AhR complex'. The receptor can still bind and interact with the same pathways and cells it usually does, but the presence of TCDD causes it to do so without the same signalling it usually requires.

Rob: Although researchers cannot study these mechanisms in humans, they have been studied in animal models extensively, and validated by observational data, that together provide convincing evidence that TCDD induces changes in the epigenome--which can have varying effects (Viluksela, Patrizi). The animal studies *have* suggested that epigenetic mechanisms cause health outcomes including reduced fertility in males, a significantly lower male/female sex ratio among offspring, and abnormal skeletal and tissue development (Baker 38). Even though we can't

directly track changes in the epigenome, scientists are able to observe the abnormal expression of known genes to measure these effects (Baker 27).

Justin: The TCDD/AhR complex–the starting point for the downstream effects of TCDD– could act on 4 cellular processes, resulting in different epigenetic changes, that result in distinct health impacts. First, the complex can bind to 'Xenobiotic Response Elements', known as XREs, regulatory sequences in DNA that initiate expression (Viluksela 4). XREs typically only bind signaling molecules, but TCDD/AhR can bind random DNA segments and XRE's without regulation, leading to production of abnormal or non-functioning enzymes.

Rob: The AhR-TCDD complex can also alter normal patterns of histone acetylation. Histones are condensed packages of DNA in chromosomes, that are either acetylated or deacetylated to control expression. While the exact mechanism is unknown, the presence of this complex associated with random histone modifications, affecting how critical segments of DNA are transcribed (Viluksela 5).

Justin: Non-coding RNA can also be altered by epigenetic mechanisms, as changes in noncoding-RNA sequences are associated with TCDD exposure (Mannikam 2016). These RNAs regulate protein production, so even the enzymes we produce–and those we don't–can be impacted.

Angelica: Additionally, the TCDD-Ahr complex is believed to engage in what is called 'cross-talk' with other transduction pathways (Patrizi 9). This means that changes in epigenetic patterns have downstream effects that can alter even those hormonal and regulatory pathways not directly impacted by dioxin. This is why the health outcomes following exposure can vary so widely.

(STOP Part 5)

Rob: Research has also shown the changes in the epigenome is transferred exclusively by the male germline, through DNA methylation patterns (Casati et. al 2019). Both male and female children will have the same epigenetic effects that their father has, indicating that he passed on his altered epigenome (Manikkam 2012, 2, 5).

Angelica: Unlike our somatic cells, which have epigenomes that are constantly reset as humans age, human germ cells--sperm and eggs--are determined at birth from parents' germlines and go unchanged through our lifetime (Manikkam 10). This means our germline DNA sequence--partially inherited from both parents--is passed down without change. While researchers haven't identified exactly why, altered patterns of DNA methylation in the male

germline, which are unchanged across male lineages, transmit the epigenetic effects of TCDD to sons and daughters through sperm DNA: transgenerational inheritance is exclusively driven by males (Manikkam et. al 2012).

Rob: On top of the possibility infants suffer from the effects of Agent Orange simply because their parents were exposed, infants themselves can be exposed *in utero* due to the persisting environmental contamination.

Justin: This exposure puts them at a significantly higher risk of suffering from neurological and developmental effects. Observational studies on Vietnamese children whose mothers were exposed during pregnancy indicate increased outcomes including abnormal tissue development, birth defects, various diseases, and impaired growth in the brain (King 2017). Some of these effects have also been modeled in rodents: *in utero* exposure led to impaired development of the hippocampus at birth, tissue-specific birth defects, and high rates of adult-onset disease (Zhang 2018). Fetuses exposed can also develop epimutations that are permanent and irreversible, causing errors in expression that persist their whole life (Casati et. al 2019).

Angelica: Even though the ideas of transgenerational epigenetic inheritance and continued direct exposure seem to be competing hypotheses, evidence suggests that both could be occurring simultaneously--but distinguishing between the two is difficult because we can't differentiate between transgenerational or direct effects without removing affected individuals from the contaminated environment. This brings up questions about which type of exposure is in play with the specific health conditions that we are observing in Vietnamese children.

Rob: Although the nature of TCDD and its impacts on human health can't be explained with *'absolute'* certainty that's required in most arenas of research, the effects are all too clear: 2.8 million U.S. Veterans and 4 million Vietnamese veterans and nationals were exposed. In the U.S., nearly 1.2 million of these Veterans either died, developed chronic illness and disease, or had children impacted by Agent Orange (Veterans and Agent Orange 2018). And in Vietnam, there was a much greater human toll: 400,000 killed or maimed immediately from exposure; 1 million either disabled or sick due to Agent Orange--100 thousand of whom are infants; and up to 1 million deaths (Anand et. al 2015)

Justin: The list of adult-onset diseases officially recognized by the VA as associated with Agent Orange includes: Leukemia, Type 2 Diabetes, Hodgkin's Disease, Lymphoma, Parkinson's Disease, Respiratory Cancer, and Prostate Cancers (Veteran's Association 2020).
In infants, listed birth defects include:
cleft palate, spina bifida, cardiovascular defects, and neurodevelopmental impairments (Mekdeci et. al 2020).

However, neither list fully encompasses all the diseases and disabilities that are reportedly common among victims of Agent Orange. We still lack a comprehensive understanding of the entire scope of diseases attributed to Agent Orange.

Angelica: Given the strength of scientific evidence explaining why generations of children born in Vietnam today are still experiencing the effects of Agent Orange, it's amazing how much there is left to understand. Human lives in Vietnam are still at a great risk, and knowing what we do about the biological threats TCDD poses, the need to act is pressing. We cannot dismiss the available information that we have, especially considering the number of lives being affected.

INTERLUDE 1

Rob: Inside the clinic, the woman lays on her back staring at the black and white screen looking for the shape of her baby. Is it the cold gel on her stomach or her nerves that keep sending chills down her spine? The doctor finally settles on his angle and lets out a sigh. She shuts her eyes tight, but finally relents and looks at the image on the screen.

Angelica: She's at a loss for words, stunned by the decision that lays before her. The baby growing inside of her has water in his head.

Justin: "It has hydrocephalus," says the doctor. The child would probably live through the birth, but might not live a normal life after. Treatment could help, but there is no cure. The hydrocephalus is simply too severe, and would likely limit the child's mental faculties, to the point that it might not be able to live life as a full person.

Angelica: The doctor somberly recommends that she get an abortion, but the longer she waits to decide, the more dangerous the abortion might be. He asks if she has any questions. But she has so many, she doesn't know where to begin.

Rob: Why is this happening to her? Why does she have to make this decision? How does she make this decision?

ETHICS & CULTURE 1

(This section of the podcast relies on the book Haunting Images: A Cultural Account of Selective Reproduction in Vietnam *by Tine Gammeltoft)*

Justin: How does a biological agent used in a decades old war affect the social and ethical considerations in the contemporary world?

Rob: What we can first understand is the culture of reproduction and gendered expectations that permeate Vietnamese society. In any case, it is difficult for a mother to decide to abort their growing child, especially so late in a pregnancy and considering the immense importance that a child represents to women in Vietnam.

Angelica: In Vietnam, family and belonging are prominent values in society. Many people believe that a child's connection to the family begins before birth. For many families, the fetus is already a human being involved in their lives. It demands love and care and is already forming relationships with its parents, family, and the world. Even though it is still developing and has no legal standing, its potential as a human is the basis for its social standing.

Justin: This connection emphasizes the difficulties of deciding whether or not to get an abortion. Parents, especially the one carrying the child, are thrown into moral and emotional anguish when faced with this decision. They must decide what is right and in the best interest of a child that has yet to be.

Rob: Not only is there existential and moral distress over the actual decision, but also over the diagnosis itself. It brings up discussions about responsibility. Why is this happening to their baby and who is to blame?

Angelica: Along with the scientific reasonings, like genetics or toxins, there are also the spiritual reasonings, such as ancestral or cosmological punishment. Oftentimes, the woman bearing the child is considered the most at blame. When a baby is found to have problems, the conversation turns to the shortcomings of the mother. Maybe she took showers that were too cold, ate the wrong food, or treated people so poorly to deserve this. Being faced with such a decision over her child forces a mother to consider the social consequences that might befall her, including criticism about her capabilities and even threats to her social standing.

Justin: In this patrilineal society, a woman's belonging to her husband's family is dependent on her ability to produce and raise a child. Her success will determine her membership into the community and her social existence. Childbearing is one very important social act that a woman does to assert her belonging into the web of society and the kinship of her family. When a woman cannot successfully produce and raise a child for her family, the emotional and social consequences to her are immense.

Angelica: What about men in these circumstances? Birth defects are *not* only caused by exposure in pregnant females, especially given that male sperm could be a site of epigenetic modification from TCDD. In the U.S., we've seen veterans publicly bear a sense of reproductive and biological responsibility for their children's birth defects due to Agent Orange exposure

(Reagan). Male bodies are just as vulnerable as women's bodies to TCDD exposure, so surely Vietnamese men socially share reproductive responsibility with women when it comes to birth defects, right?

Justin: Unfortunately not, due to traditional expectations for women in Vietnam…

Christina: "[00:16:18] It would easily mean in that culture that she's failed. It would be an immense sense of failure. She would think that something's wrong with her. She's been, on a religious end a lot of them would believe that they had been punished by the gods like something that they've done wrong. It could potentially in some families mean shunning… That's how, that's sadly how straightforward it is, you know?"

Justin: There is an extreme pressure on women to be successful childbearers in Vietnamese society. They must establish their and their child's place in society. It is on these social factors that Agent Orange is hugely impactful–if it truly affects the germline, then it changes who these people can be and how they are accepted.

INTERLUDE 2

Rob: The woman numbly walks home from the clinic, afraid to discuss what she learned with her husband and her family, terrified to even begin thinking about the choice she has to make regarding her child's fate. She's at the front door now, her cold sweat signaling her hesitation to go inside and face them. She takes a deep breath, and opens the door, only to find her sister-in-law and mother-in-law. She feels a little more comfortable talking to them first. They're older than her and could provide some wisdom.

Justin: She asks her Sister-in-law what she would have done, who told her:

Sister-in-law (*Haunting Images,* 97): This is something that I can only think about now. When I was pregnant, it would have been difficult for me to talk about this. All I felt was "This is my child and I don't want to give it up." But if the fetus had had a defect, an obstetrical intervention would have been better than letting it suffer in the future…

Justin: Her mother-in-law follows, saying:

Mother-in-law character (*Haunting Images*, 77): I think that in order to live, a child must be complete like other children. If the child simply lies there, or sits there, or does not understand anything… then it means a lot of suffering. Then it is better to be brutal right from the beginning. Of course, that will be very painful. But I still think it is better than letting the child live. It will

lead a life of suffering. The child is the one who will suffer most. As a mother, you live only for a short while and then you die, but the child will suffer for much longer.

Rob: The woman suddenly asks,

Angelica: do you think I'm poisoned?

Rob: The two older women answer her with silence. None of them are sure. But an unspoken cultural truth is apparent for all of them: the child growing inside her probably would never grow into a full person.

ETHICS & CULTURE 2

Justin: Because family and belonging are such strong values, it is important for a person to be able to actively form social relationships, both with family but also with strangers through everyday interactions. This allows a person to establish themselves in the web of connections that make up society. This is embodied in the idea of personhood. In order to be a full person, one has to be able to participate in social activities and contribute to society. Any other way of being means that the person is not truly living a life and will only suffer. If they cannot reciprocate sociality, they will live their lives on the margins of society. Following this belief, many families find it better to abort a child that they believe will not become a full person because they believe it in the best interest for the child.

Rob: Woven into this perception of personhood are capitalistic political and economic motivations. Following decades of family planning programs to manage population growth, the Vietnamese state began to turn attention to the quality of the population. Family planning advertisements equate the successful production of families to loyalty to the nation. Hidden within this state propaganda are the capitalistic benefits of an able bodied population. By encouraging healthy families and children, Vietnam ensures that they have a strong and able workforce in order to be competitors on the global market.

Angelica: In a society that is already permeated by the process of selective reproduction, how does this toxicant with a growing association with birth defects affect public perception? In other words, how does Agent Orange play into these ideals of reproduction and personhood? The health effects of Agent Orange were not publicly discussed. The Vietnamese government was very worried about their image on the global market–their products could not be seen as tainted or poisoned. Additionally, Vietnam did not want to jeopardize their growing political relationship with the U.S.

Christina [00:07:52]: “I feel like the Viet government frequently does that actually where anything related to the war or anything related to Agent Orange shouldn't be talked about. It's a shame if you do.”

Justin: However, by the mid-1990s and early 2000s, the stories about Agent Orange began to emerge in public media. There were films and articles that told the stories of Agent Orange families, as well as non-governmental organizations dedicated to supporting victims. The images of Agent Orange victims made it into mass media and were shown everywhere. This subtle threat of birth defects encourage women to get regular check ups and work even harder for the prenatal care of their baby. The emotions and fear that surrounded the growing controversy of Agent Orange helped establish state interventions towards their objective for an able bodied workforce.

Rob: It is also worth noting that this attention to Agent Orange does not seem rooted in justice. Families that are thought to be affected by Agent Orange still do not receive adequate resources to help with their medical and social burdens. In fact, the attention given to family planning seems to harm the most marginalized and vulnerable of Vietnamese society, women and the disabled. For women, problems with reproduction and birth defects fall on them to bear. The imagery of Agent Orange victims burdens women with the task of making sure they and their children are healthy, yet does not offer assistance to deal with exposure. The state raises Agent Orange as a pressing issue without pairing it with an adequate system of justice and resources for the community of the affected. It represents more of a warning of all the bad things that can happen to a child if a woman doesn’t get regularly checked throughout her pregnancy and ensure the child’s health.

Angelica: But culture is not the only obstacle in the pursuit of justice and resources. One problem lies in the fact that people are hesitant to accept causation based on studies done on animals. However, as Dr. Pelligrini explains, there is no reason that the biological impacts would not also be plausible in humans.

Dr. Pelligrini [00:22:19]: if you could show that convincingly, then I think it's entirely plausible that the same mechanism would occur in humans at this time. At the basic biology level, there's essentially no difference between a human, a zebrafish or a mouse. So any mechanism that you identify that could explain this persistence in those species could very well translate to humans.

Justin: But while we’re taking decades to accept this evidence, the consequences will only compound with time. The community of affected will only get larger:

Dr. Allard [00:29:05]: think about the number of generations that are impacted. So you delay action, decision for a decade. How many more people, locally I suppose, and how many generations later if indeed transgenerational inheritance is taking place here, but potentially how

many more generations are impacted? So that's what always whenever I talk about transgenerational inheritance, I say that we don't necessarily have all of the evidence, we don't really know exactly how it works, but we know that in some cases it does happen. And just as a precautionary measure, we probably don't want to delay action because the repercussions are so long-term. Let's just act now. It's just an impetus to just not delay.

Justin: What stands in the way of action is a dominant paradigm of genetic determinism in the study of disease, which initially directed Agent Orange research. It asserts that biology is determined by DNA, and that disease can ultimately be traced back to defined changes in our genome. The problem with this is that extremely small amounts of disease are associated with, or traceable by genetic abnormalities. On the other hand, most diseases are caused by environmental pressures that impact the way DNA is expressed (Skinner 2019). So, most researchers are committed to the idea that there has to be proof of detectable mutations in DNA when someone is suffering from a disease or birth defect associated with Agent Orange, even though this finding proof may not be possible.

Rob: What action can we possibly take, when we're dealing with institutions that rely on a paradigm of scientific proof, of hard genetic evidence, when that's not necessarily what's even important. There's more at stake, and by the time we actually have better evidence, it might be too little too late for those affected.

Angelica: We need that paradigm shift, we need the research community to widely accept that this is something that needs to be researched even if there isn't hard proof. Without the ability to directly model epigenetic diseases or illnesses in humans, the scientific community must confront its priority: focusing more on fully elucidating the mechanisms in humans, or focusing more on preventing further harm to affected people in the face of uncertainty.

INTERLUDE 3

Justin: The Vietnamese woman grapples with herself, frustrated that she cannot yet decide on what to do. Maybe she should keep the child, and learn to care for it. One of her neighbors did the same, maybe they have some insight on raising a disabled child with birth defects likely from Agent Orange. She pays them a visit.

Angelica: Mother character (*The Children of Agent Orange*, 00:15:06-00:15:28): My son is sick all the time. Because of that we cannot work. Being in the hospital all the time, our family is suffering. We've had our hearts broken. We've reached our limit.

Justin: She knows they are struggling to cope with their son's heart condition. He is in pain all the time, he can't even lay down. She asks if there is any treatment they can get for him. Maybe a heart transplant?

Rob: Father character (*The Children of Agent Orange*, 00:13:30): The doctor said it would cost billions of Vietnamese dong [about 40,000 US dollars]. It's impossible for us.

Justin: The woman asks:

Angelica: Why did this happen to you? Why is this happening to me?

Father (*The Children of Agent Orange*, 00:13:44): I think it was when I was a soldier and we set up base in an area full of poison. My two sons are both affected.

Justin: She walks away from their conversation more confused than before, more unsure in what her final answer might be. The doctor said there might be treatment that would work for her child. But would she ever be able to afford it? Why would she have to bear this burden if it was not even her fault? What if she did have some exposure to the dioxin–who could she turn to for help?

LAW

Angelica: If Agent Orange is implicated in such a huge controversial health issue, why is there nobody taking responsibility, and why are there no resources for the victims?

Justin: In order to answer that question, we would need to consider the legal and political history of Agent Orange. After the Vietnam War, veterans that sprayed and were exposed to the herbicide as a part of Operation Ranch Hand began to develop health conditions that were related to their Agent Orange Exposure. In 1984, almost 10 years after the end of the Vietnam War, a group of veterans filed a lawsuit against the chemical companies that produced Agent Orange, including Dow Chemical and Monsanto. Seven companies settled out of court and paid the veterans over $100 million but still denied any responsibility.

Rob: Despite not admitting causation, the U.S. then passed the Agent Orange Act of 1991, which allowed Vietnam veterans to be compensated for certain medical conditions that were associated with their service, particularly their service that involved them with Agent Orange. This was considered to be a success for the veterans. They were able to get some type of recognition for the conditions due to their service, but they were still unable to get any admittance of liability from the government nor the chemical companies.
(Gammeltoft, 2014, Miner, 2009, Palmer, 2007)

Angelica: In 2004, nearly 30 years after the war, the non-governmental organization Vietnamese Association for Victims of Agent Orange, which we'll call VAVA, filed a lawsuit against the chemical companies that produced Agent Orange–a case known as *VAVA vs Dow Chemical et al.* VAVA argued that the defendants were guilty of violating international law by providing the government with a poison, Agent Orange, to be used during war. The case was dismissed in 2005 by Judge Jack Weinstein from the Federal District Court in the Eastern District of New York. He held that because the U.S. did not ratify the Geneva Convention that banned that use of poison in war until 1975, after Agent Orange was used, they were not in violation of any law. (Uesugi, 2013, Palmer, 2007)

Justin: And because the use of Agent Orange did not violate international law, the chemical companies were protected under the government contractor defense, meaning they could not be sued for manufacturing and supplying the herbicide. Additionally, based on the definition of poison at the time of its use, Agent Orange did not qualify as one. Judge Weinstein adhered to the understanding of poison based on intention and dosage. The use of the herbicide was not meant to hurt humans, nor was the concentration of the dioxin contaminant in Agent Orange high enough to be considered a dangerous dose. (Uesugi, 2013, Palmer, 2007, Roth, 1984)

Rob: Poison? There's that word again. Does it actually mean anything?

Angelica: It must have meant something important if it was used in court as a framework to dismiss the *VAVA vs. Dow Chemical et al.* case.

Justin: But, it's just so… I don't know. It seems so subjective to rely so heavily on such a vague term for such an important case. Imagine that, delegitimizing the narrative of the Vietnamese woman we've been following, the one with everything to lose, all due to technicalities and seemingly arbitrary decisions about what poison actually means in the grand context of Agent Orange.

Rob: What do you think, Dr. Allard?

Dr. Allard [00:17:46]: "I'm sort of shocked by how unscientific it seems sometimes where you do experiments in animals, you try to figure out what seems to be a safe level for animals. And then you take that value and you divide it by one thousand and you say that that value divided by 1000 is what's safe in people. And there's a rationale behind this. So by 1000 factor, which they call the uncertainty factor. It's simple to take into account the difference between animals and humans. Sorry, animal models and humans and the difference between people as well, because some people will be more sensitive than others. But are we sure that 1000 will encapsulate every

difference? It just seems a little bit, I don't know. Random in a sense, right? Arbitrary is the term I was looking for. So the whole way that we assess it and we tried to come up with a clear cut line of that dose is safe, anything above it is not going to be. It's still really archaic, and a little bit arbitrary."

Rob: When we consider the *VAVA vs Dow et al.* case, a big part of the reason their case was dismissed was because the convention that prohibited poison in war did not technically cover the time that Agent Orange was used. But we are still seeing real and ongoing consequences. Should we and how can we adhere to a legal system that is still trying to catch up to changing scientific knowledge, especially in terms of long lasting, multigenerational harm?

Dr. Allard [00:32:16]: "... you have all this framework that we're not just ready to think about. Or we're ready to think about it, but we just don't know how to deal with that, right. That's super, super long-term stuff. Our legal framework is not there. So we have to really stretch ourselves and think about a framework where we take that kind of stuff into account. We need research first to show, yes, it's real. It's pervasive. It's you know, it's a real issue here that we need to act on. And then we can, then we have enough power, leverage to push people to think about how ethically, legally, economically, you know, toxicologically at all levels, we need to think about those extremely long-term consequences."

Angelica: Currently, the U.S. still has not taken responsibility for the health effects associated with Agent Orange exposure, but has started clean-up efforts at former Agent Orange storage sites which are dioxin hotspots. In 2018, they began clean up efforts at the Bien Hoa Airbase following the completion of clean-up at the Danang Airport (Martin 2019).

Justin: It is also important to note that in Congressional Service Reports, which are prepared to help Congress make decisions including ones surrounding Agent Orange and aid to post-war Vietnam, reporters stress that providing aid is not an admission of responsibility or liability for the effects of Agent Orange. In fact, they emphasize that the money that they send to Vietnam is solely humanitarian aid and helps establish the U.S. as a soft power in Asia, aiming to influence the countries through non-military engagement.
(CRS 2012)

Rob: How did they phrase it again?

Angelica: As of 2019, Congress appropriated "not less than $20,000,000" for Bien Hoa cleanup efforts in collaboration with the Vietnamese government. In addition, Congress also appropriated "not less than $12,500,000" for health and disability programs in dioxin hotspots and Vietnamese areas sprayed by Agent Orange (Martin 2019).

Justin: That's nothing! They aren't taking true responsibility for anything that they've been accused of. Not only is this just a small amount of resources for a serious issue, but also there is no admission of culpability.

Rob: So what would accountability look like? More funding? Reparations even? What could possibly be done to right a wrong that continues to fester in silence. What is the answer?

CONCLUSION

Angelica: What is the answer, the Vietamese woman thinks to herself. There are so many questions running through her head, so many mixed emotions, with nowhere to turn to for full support. No matter how hard she tries to find one, there is no good answer. And that's what it is at the end of the day, *uncertain.*

Rob: The case of Agent Orange is messy–muddled from decades of neglect and uncertainty. This year, we look at half a century since the end of Agent Orange use in Vietnam. But for many, that end only marked the beginning of half a century of medical problems, familial stress, distrust, and uncertainty. And based on the state of science and legal affairs, there does not seem to be an end in sight.

Angelica: While it is true that there is still a lot we cannot determine about Agent Orange, the controversy has still revealed the shortcomings of the frameworks relied on in this case: genetic determinism, evasion of legal accountability, and a patriarchal culture with little support for the marginalized. All are unable to properly address the human toll of those affected in Vietnam.

Justin: The word *poison* flutters by in the Vietnamese woman's imagination. She asks herself, *am I poisoned?* If the child growing inside me is the way it is, does that mean that *I* am doomed? Will I never be able to have a family? Was I not careful enough? Maybe I really am poisoned.

Rob: She pauses, and then speaks to her unborn child. What can I do? What *should* I do?

Angelica: There is no answer. She notices the fog in the distance once more, the old airbase completely out of sight.

Justin: She thinks, maybe that question, that word… poison. Maybe it doesn't matter. Because at the end of the day, even if Agent Orange was never meant to be a poison…

Christina [00:17:27] "… it has the effects of a poison. And it's having the effects generations down and it should, it's something that needs to be treated. You need to find any solutions that

you can. And if not, you can't if you can't find any solutions you need to treat the effects of it, meaning these deformities, give them good homes, give them medications to ease their pain."

Rob: The Vietnamese woman wishes she had solutions to turn to, answers.

Angelica: But she has to make a choice with no right answer, a burden that she must silently carry.

Justin: She looks up. The fog is getting closer, an old streetlight illuminating it with a sickly, orange hue.

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Interview Transcripts

Dr. Allard Interview (2/25/2020)

Dr. Allard [00:00:02] So can you remind me what this is for?

Justin [00:00:09] Yes. So this is for our Soc Gen 108 project. So we're focusing on Agent Orange in Vietnam and how reproductively toxic it is. Like it has it. It has very it looks like it has a very clear transgenerational effect in terms of severe birth defects in the those who are exposed to Agent Orange in some way. And we're sort of parsing through the ongoing controversy of it,

because you as we've found a lot of our research, a lot of the scientific literature is unable to establish causation, causation between Agent Orange and birth defects. Even though there's a lot of correlation and there's also a lot of ethical and legal issues that would go into establishing causation. And yeah, so so so there's a lot happening. And we think that your perspective with BPA research in particular really useful for helping us understand like a more scientific perspective of like like a controversial topic.

Dr. Allard [00:01:27] Yeah. So I wish I actually knew more about Agent Orange per se. Actually, I do not know very much at all about the transgenerational effects of this, so before before I announced that I just want to maybe modify something that you said about transgenerational and go back to the lexicon that's used around around transgenerational versus multigenerational. So, or inter-generational. There's a lot of words sort of used in the literature and that can be sort of confusing. So nowadays more and more people use the term transgenerational when they mean something that is not the F1 or the F2, but it's actually beyond that.

[00:02:20] That would mean that somehow the germ line got, so the germ cells that you assign in the sperm got through exposure, got modified in a way that will make people that derive from the experimental science somehow. I think this is when you see the very next generation being impacted, like what you're describing here. You don't have to use the term transgenerational because this could be the direct effect of exposure, especially if the mother was pregnant during the exposure, the babies that were born could have been directly exposed to Agent Orange. And so it's not something that's passed on from generation to generation. That was if a baby is born with birth defects and the mother was exposed during pregnancy, that's in fact an impact of exposure, it's not passed on from generation to generation. So people don't use in that context the term transgenerational inheritance.

[00:03:29] Having said that, what I thought was absolutely fascinating is I think the same day you sent me that email, I received a request that was sort of passed on between different doctors from someone who wanted to actually look at the transgenerational impact of Agent Orange and said that he worked with communities in Vietnam. And now it's been so long that they actually have seen that in the field that now they've seen that it's not just that first generation, but actually several generations of people seem to show higher rate of birth defects and other issues.

[00:04:14] And he wanted to get guidance on what should we look for, if this indeed is transgenerational. Is there something molecular that we can look for? It would allow us to say yes that birth defect shows that molecular signature of an exposure to Agent Orange. And the problem is we're not there yet. And I think that's ultimately where the controversy comes from, is that in animal models, we can get causation, in humans, we most of the time cannot, right. We

can have very strong suspicions, very strong indications. But getting to the true causation is difficult. So you switch to animal models and you try to get there. But but when we do this, we have the animal model work and we don't necessarily know what to look for, the molecular level in people. That would be that would be. So I don't necessarily have a good answer for you, except for saying that what you're describing is an issue within the context of Agent Orange is a very common issue in the field of epigenetics in general, and transgenerational inheritance, which is the fact that we have all these correlations and we have very little understanding of how it works. And therefore, we don't know whether these correlations mean causation or whether they don't, even in animal models.

[00:05:50] So I think a lot of the work on multi/transgenerational inheritance, a lot of the work done in animal work, in animal models has been correlative more than it's been causative. I think in a few years the field will have an advance where we'll understand all these relationships so much better that we'll clearly understand what has been historically correlative and what has been causative. But we're just not there yet. So I think those debates will remain there for a while until we all move the field forward to the point where we can really say, yeah, this is causation or that's correlation. Does that make sense?

Justin [00:06:36] Yeah. Thank you. In your BPA research, were you able to establish causation in your C elegans model?

Dr. Allard [00:06:48] We did. We did. And we're not the only ones. So I work, as you said, we did do our work with worms. And the reason why we wanted to work with worms is because, one, the genetics is very well-characterized and two, they are extremely practical as a model system.

[00:07:05] We can quickly intervene. Genetically, they have a short generation time so we can look at things that evolve over several generations and intervene at different points, to try to prevent things from being passed on from generation to generation. And that's how you show causation. If you have something molecular that's happening and a disease, well then try to prevent the molecular thing from happening and try to see if that prevented the disease. That's going from two different correlations to actually pretty causation. And that's exactly what we did with C. elegans. So we had BPA exposure, we knew that it was messing up reproduction over many generations. But then we also had a molecular signature, specifically modifications of the epigenome. So that molecular information that's around the genome that modifies gene expression.

[00:07:59] And we knew that BPA created a very specific signature of the epigenome, that by playing with enzymes to regulate it, we could try to revert back to what we thought was normal state. And when we do that, we prevented all the reproduction issues from happening, for

several generations. So that told us that, yes, there was definitely an active relationship and that BPA was probably causing and I'm being cautious or scientifically cautious, but I want to say, really that BPA was causing those reproductive effects over many generations by modifying the epigenome. So that we could do really quickly and easily and almost I wanna argue beautifully, elegantly in a word.

[00:08:47] But that's also where the field now is, one more moving forwards. Whether it's with worms, with flies, and to some extent more and more in the mouse as well, there's techniques that are developing that allow people to actually directly interrogate the epigenome.

[00:09:03] Actually using CRISPR/Cas9 to not modify the genes, but actually modify the epigenome itself and then figure out whether that prevented the disease from happening or not. So that's what I was alluding to earlier, that the field is developing technologies to really go after causation. It's stunning to get employed, but not everyone is there yet. But hopefully in a few years, we'll have. We'll have moved there. I think ultimately what we need is a collection of different approaches where people will work in small, small model organisms like mine, like C. elegans or flies that reproduce very quickly.

[00:09:47] Well you can sort of get an idea of what to go after. Because the epigenome is a very large lexicon of different chemical modifications, that change gene expression. So so there's so many things that you could try to go after and so expensive and long during the mouse. So let's try to figure it out in small organisms. And once you figure out a little bit then that directs, what you go after in animal models, in larger animal models. And then once that's all confirmed, then maybe then you can look for the same molecular signatures in human populations. And it's also an advancement of the research where many, many years ago people had the foresight of setting up epidemiological cohorts where they decided to try to set them up for many generations.

[00:10:41] And so we have a famous one in Denmark, where they are now at the F3 generation. You have actually another one in California. Barbara Cohn at the University at Berkeley has also paid over three different generations. And I think Trimingham as well. Another study anyway. There's several studies around the world now that have followed families for several generations. We are, we as the scientific community, we're still like pouring ourselves over that kind of data and trying to see what what holds, what doesn't hold. But it's kind of all ready to, for other people to come in and look at those molecular signatures. We just have to know what to look for. We don't know just yet. They will be more correlative, but if you have the animal work and then you see the same molecular signatures in humans. That would be a very strong, very strong, I don't know, evidence that those things are legit and relevant for the human experience, did that make sense?

Angelica [00:12:01] It sounds like you really have to kind of start from the bottom in order to work up to what you're really trying to look at, like starting from the most simple models from to C. elegans to rats, then to humans to establish like some causation or correlation, as you're saying.

Dr. Allard [00:12:16] Yeah. I mean, that's I'm biased in my way of thinking because I do value very strongly those smaller animal models. There are other ways of thinking about this that does not involve smaller animal models, especially because there are biological differences. And so some I would argue more old school researchers would argue that why bother? I understand that it's faster in smaller animals, but why bother? Since the biology is different, it just works in mice. And even if it takes 10 years to figure it out in mice, at least it will be more relevant to humans. I think there's so many things as a field that we still need to figure out that any piece of information is useful, even in understanding in what ways these animals are similar and in what ways they're not similar.

[00:13:16] So that then we know that we can at least model this bit in that animal and that bit in another animal if that makes sense. I think any kind of information of how any kind of exposures get the effects of that gets passed from generation to generation, I think we still need to figure that out as a rule if any model isn't very well. So. So I guess I believe in that tiered approach or multi component approach, whatever you want to call it. I think we need that comparative biology.

Angelica [00:13:57] So you have like this type of you're saying as a field we need to be learning more and kind of evolving sort of. One of the big issues within the case is the idea of Agent Orange as a poison or not a poison. So like speaking generally, your research and maybe paralleling it with Agent Orange-like dioxins, would you consider BPA poison? How do you define a poison?

Dr. Allard [00:14:22] Yeah, I don't actually use the term poison. I use the scientific word of toxicant, which is different from a toxin. Toxin is naturally produced, a toxicant is thought to be manmade, not naturally made. But that still has a biological impact.The poison, you know, could be a colloquial term to refer to all of this.

Angelica [00:14:55] Sorry to interrupt. Well, it basically comes like the legal aspect of Agent Orange. It's use in the war was dismissed as a war crime because it wasn't considered a poison in the sense that it was intentionally administered to harm people. But because of the effects that we've seen from it has toxicant-like effects on human beings. There's just been this shift in the idea of what we should consider as a poison like socially and legally. We're just wondering, like

what your thoughts might be on this definition of poison, like how it has shifted, if that's related to your research in any way.

Dr. Allard [00:15:33] No. I mean, I think what you're talking about is a much larger, it's a very important, but much larger conversation about what is safe and what is not safe in general. And there's so much gray in that. That's a very hard question to answer. So you may have come across examples or news bits of people running marathons and just drinking water and they actually end up dying of that water intake because they actually not replenishing the electrolytes that they are losing by running, right. So in a way, too much water can also be a poison. Right? You can you could try to frame it that way. I think it's a little shaky. But the bottom line is that the one of the mottos used in toxicology is "dose makes the poison," meaning that anything at a really high level is probably going to be bad for you. Now, there's like some new frameworks that have appeared that also say sometimes even ultra low dose can also be bad for you. Sometimes a high dose as one effect and very low doses another effect. And in-between sometimes you're OK, we have like some evidence for some chemicals that can behave that way. Endocrine disrupting chemicals seem to be acting, some cases at ultra-low doses. But in general, there's still that framework that "dose makes the poison." So for me, it's not a question of what is a poison and what is not poison. It's really what is the safe level and which you can be exposed and what is and therefore what is not the safe level. And this is the work of risk assessors. People work for the EPA, for example, that have to come up with a number that say, if you're below this, you should be fine. If you're above this, you are going to start having concerns about exposure.

[00:17:46] And it's really tough work. And it's just sort of the process, as I'm learning more and more about, I'm sort of shocked by how unscientific it seems sometimes where you do experiments in animals, you try to figure out what seems to be a safe level for animals. And then you take that value and you divide it by one thousand and you say that that value divided by 1000 is what's safe in people. And there's a rationale behind this. So by 1000 factor, which they call the uncertainty factor. It's simple to take into account the difference between animals and humans. Sorry, animal models and humans and the difference between people as well, because some people will be more sensitive than others. But are we sure that 1000 will encapsulate every difference? It just seems little bit, I don't know. Random in a sense, right? Arbitrary is the term I was looking for. So the whole way that we assess it and we tried to come up with a clear cut line of that dose is safe, anything above it is not going to be. It's still really archaic, and a little bit arbitrary. And I'm not super happy with that. So I think that's the gray that I think I would want to speak to. The thing that would still have a hard time coming up with is a really clear safe dose as opposed to coming up with what is a poison not a poison. It's at what dose. Anything. Is a poison or toxic, or not toxic. I think that's the concept that we're still very, very much struggling with, especially because we have so many chemicals out there that we don't have that much

information to even come up with the same. It just sounds like it's pretty, pretty shocking. Yeah, that would be my answer to your very long question.

Angelica [00:19:50] That was good, I think that was good, that was a good answer.

Justin [00:19:51] And sort of building off that, while now at least like we can observe like a lot of manufacturers of plastic products saying oh, BPA free. Was there was there a period before like before, like, that establishment of causation where it was just more correlation. Were these chemical companies and manufacturers like tried to in a way take advantage of that gray area? You were speaking to to sort of sort of dissuade the uh...

Angelica [00:20:24] Like any pushback, to your research. Yeah, basically like politically or socially.

Dr. Allard [00:20:30] Yeah. I think the push backs are are evident. Let me see. So I think I think the competing interests in the industry when the world of toxicity are obvious and I think they can take different forms. For example, many years ago I wanted to collaborate with Dow, who is a chemical company...

Angelica [00:21:08] They actually produced Agent Orange.

Dr. Allard [00:21:10] And they produce BPA as well. And I wanted to collaborate with them to investigate BPA. And they said, we should choose another chemical because we're not going to look for, we're not going to invest our money to do research on something that we produce, which I understood, but at the same time, like, but don't you want to know? Right. So there was that tension there.

[00:21:37] And then there's a very famous example about a consulting company called the Weinberg Group, where they produced these these letters that they would send to potential clients, which were chemical companies, and they were offering their services. And in that letter, they actually list the type of services that they offer. And that was services they were offering was the publication of white papers that would muddle the scientific consensus. So it would write papers, try to publish them and would go against what other people have shown. So if people had shown, scientists had shown that show that Chemical X was toxic, then they would publish papers to the opposite. And then at the end, there would be no scientific consensus.

[00:22:34] Another one was trying to create information to where there were communities affected by a particular spill, a particular chemical or some sort. Whatever way. They would create town halls and focus groups with the local communities to inform them of the risk. But it really basically was trying to convince them that everything was fine so that they

would not sort of self-organize beyond this and create a movement. They would try to kill the community engagement and movement right from the beginning.

[00:23:16] Yeah. They had a whole other list of ways to sort of alter the course of things. And I can't remember all of them now, and I thought that was really shocking because it highlighted sort of the underside, the dark side of. So that was a consulting company that was not necessarily a chemical company itself. But I felt like it still highlighted. It spoke to a darker side, to the whole business of the chemical industry. And you don't know if that's just one thing that transpired. You just don't know how many other things have not made it out there that we don't know about. Right. So it just made me a little bit paranoid for a while, what's going on out there.

Angelica [00:23:57] That kind of reminds me of like what they call the Tobacco Strategy, where they have non-relevant scientists publish pieces about, you know, tobacco being safe, and just really just try to confound what the public information is.

Dr. Allard [00:24:11] Yeah. Yeah. Oh, and I had I also went to this meeting where they talked about diet sugars and it was really interesting because they had a press session about the efficacy of diet drinks. And one half of the researchers were not sponsored by PepsiCo or other organizations and the other half were sponsored by them. And the first half showed that diet drinks physically do not lead to weight loss. If anything, the effects were actually weight gain. And then the other half sponsored by the industry showed that that led to weight loss. And you're like, well, then what is real? The bottom line is that the experiments were actually set up differently. And, you know, one has to think, well, which which experiments were set up the best. And I think the answer was that the one set up by the academic researchers, not sponsored, were set up in a more real world scenario, whereas the other ones set up by the industry were set up in a way where food intake was extremely controlled. And so in that particular environment, extremely well-controlled conditions, then there was a big loss. But if you leave, if you let the animals kind of be, then they end up eating more and actually gaining more weight, which is probably how we would do it, right. So so you could see how there was a bias even in the way that things were set up that would lead to different outcomes. So all these things together, you know, I don't necessarily have this very specific killer example, of "yes, this happened with BPA, or that happened with Agent Orange." But you can see how there's different interests at play, and how science can be so incredibly biased based on what your interest is.

Angelica [00:26:06] That's definitely something we've come across in some of the studies we've looked at with Agent Orange and dioxins. Specifically like studies on veterans, Vietnam veterans about exposure, where they looked at Vietnam veterans that weren't even exposed, and they're like there's no association because, look, there's no birth defects. But if you look at where they

were coming from, there wasn't even exposure. It's definitely something that we're trying to unravel.

Dr. Allard [00:26:30] I'm just I'm just shocked that anyone would contest how incredibly toxic Agent Orange and dioxin are, and because it is so well established in the world of toxicology. Dioxin is a, I mean, it does many things but ultimately will lead to the activation of AhR, but also anyway, mutations. So you expect you see a whole host of things happening downstream in the next generation. Beyond that, I'm not sure. But at least in the next generation, you would expect, based on everything that we know, you would definitely expect that kind of thing happening.

Justin [00:27:04] Yeah. And and culturally, at least in Vietnam, that sort of transgenerational expectation is there, because like even if, based on the literature we've read, even if, Vietnamese women in particular, like they themselves would not have direct exposure to Agent Orange, like there is sort of a underlying paranoia about having a lot of ultrasound scans, excessive amounts up to, what was the number? Ten to eleven?

Angelica [00:27:34] Yeah, just way more than you do. You're only supposed to have like a couple during pregnancy. They they're getting like regular checkups for ultrasounds.

Justin [00:27:45] Just to verify that their child doesn't have birth defects. And it also does intersect with a culture of sex selection in Vietnam. But like Agent Orange is also a driving force there too.

Dr. Allard [00:27:57] But it's, correct me if I'm wrong, but Agent Orange is an extremely, oily mixture, right? is it?

Justin [00:28:04] Yes.

Dr. Allard [00:28:05] I thought it was extremely oily because it's supposed to deposit on foliage.

Justin [00:28:11] It sticks really well to biological materials.

Dr. Allard [00:28:13] Which is why it bio accumulates, that's what I'm going for. So what I'm saying is that it doesn't really matter whether you've been directly exposed to it or not. It's going to be everywhere, well in the food, and...

Justin [00:28:26] Not everywhere necessarily, but particularly in what are called dioxin hotspots, which are a former U.S. air bases that stored thousands of barrels of Agent Orange, where contamination is very, in the current, there's many throughout Vietnam. Only one has been cleaned up there. Currently, the second big one is being cleaned up, which is Bien Hoa air base.

Dr. Allard [00:28:50] Isn't that crazy that so many years later.

Angelica [00:28:53] They didn't even start until 2012, which is like when they first did the Da Nang airport one. Yeah. It's like decades long and a lot of political fighting honestly that went into that decision.

Dr. Allard [00:29:05] And think about the number of generations that are impacted. So you delay action, decision for a decade. How many more people, locally I suppose, and how many generations later if indeed transgenerational inheritance is taking place here, but potentially how many more generations are impacted? So that's what always whenever I talk about transgenerational inheritance, I say that we don't necessarily have all of the evidence, we don't really know exactly how it works, but we know that in some cases it does happen. And just as a precautionary measure, we probably don't want to delay action because the repercussions are so long-term. Let's just act now. It's just an impetus to just not delay.

Justin [00:29:51] Yeah, yeah, yeah.

Dr. Allard [00:29:56] Anything else, do you have more?

Angelica [00:29:56] You answered a lot of them without us asking, so.

Dr. Allard [00:30:00] Yeah, I'm a talker.

Justin [00:30:08] I guess. I guess maybe to to wrap up. Why is it important to study intergenerational or transgenerational effects?

Dr. Allard [00:30:19] For exactly, the reason that I said, that. I mean, I guess that's a good summary of everything that we talked about. It's important to study it, to really understand. Well, how it works, but more importantly, for practical purposes. Do all chemicals cause transgenerational inheritence or only some? And that answer is super important because then you would want to phase out right away, those chemicals that have extremely long-term consequences. And we're not at the stage yet where we have even that kind of answer, right. We know that some of them, like tributyl-10, for example, I think that's pretty clear that it has transgenerational inheritance effects in mice and rats. But we don't know, we don't know about other chemicals. So I think that information will allow us to prioritize chemicals for dealing with them really quickly and not wait any longer. And that's that's the second reason why it's important, because when you have such long-term impact, you need to be able to act now. So we need we need that information. And we really don't. We really, really don't. It's not part of the way that we've been dealing with risk, we've been dealing with risk from direct exposure, usually from, most of the time from, like parent to child. Some chemicals are studied for a little bit longer than that. But usually that's how we frame our approach to chemicals and the risks

associated with them. And if we have to revamp all of this and think about many more generations, then that changes a lot, right.

[00:32:16] We think about this from even a legal perspective in the Institute for Society and Genetics. If we, in humans, if we have to think about three or four generations, other companies will produce something hundreds of years ago still legally responsible for the effects that show up, maybe not hundreds of, you know, much, much, much later in people. Well, four generations would be one hundred and twenty years, right. So we're definitely over a hundred years. Are people still responsible, legally speaking, for something that happened one hundred and twenty years ago, or corporations, are they still responsible? So you have all this framework that we're not just ready to think about. Or we're ready to think about it, but we just don't know how to deal with that, right. That's super, super long-term stuff. Our legal framework is not there. So we have to really stretch ourselves and think about a framework where we take that kind of stuff into account. We need research first to show, yes, it's it's real. It's pervasive. It's you know, it's it's a real issue here that we need act on. And then we can, then we have enough power, leverage to push people to think about how ethically, legally, economically, you know, toxicologically at all levels, we need to think about those extremely long-term consequences.

Angelica [00:33:52] Do you think that a necessary technology is there in order to research?

Dr. Allard [00:33:56] No.

Angelica [00:33:57] OK. So it's not just framework. It's also actual like material that your working with.

Dr. Allard [00:34:02] Yeah, because like, you know that the studies that I've seen done in mice or rats, they take they take several years, they use a ton of animals. So that costs a ton of money because of the amount of animals. But I'm talking about like sometimes 300, 600 different animals, which is a lot. And there's also an ethical, ethical cost to that research, right. Like you're talking about animal use research. To what extent are we going to sacrifice hundreds and hundreds of animals? And that's per study, right. For one chemical, one goes, we're talking about 300 animals, when you want to go to the fourth generation. So how many animals are we going to kill in order to answer that question? Is that a necessary evil? Or are there other ways that we can think about that would help us prioritize so that we don't screen all chemicals in mice, rats or even even other things I'm not thinking of that don't exist yet that could think of to help us figure this out. That's why I believe a tiered approach where we start in very small animals like C. elegans, like flies. Things that we feel a bit less guilty killing. Maybe it would help us prioritize, inform study in larger animals. That's what I believe in. But we still need to really come up with real, with good assays that work really well and that are informative and predictive.

Angelica [00:35:54] Do you think that's going to happen anytime soon or is it just going to be?

Dr. Allard [00:35:56] No, I think we're going to get there. Yeah, I think we will. Yeah. Whether that gets included into the regulation framework, regulatory framework, that's different. Academia, and sometimes industry tend to be the leaders. They move forward quickly. Academia because we always tend to look for the next thing, industry because usually there's economic incentives behind it, like they don't want to have EPA later on telling them, well you've been producing this, but you have to take it away from the environment now, so you have to stop producing it. Usually they tend to be actually not always the evil guys. They tend to be more proactive because they, you know, they want to make sure that the investment carries through for many years. So usually academia and industry move fast, but it's the government, the regulatory side of the government, that tends move slow. So that's the part I'm more concerned about. When will the regulatory framework take all of that into account, that transgenerational inheritance? I'm not sure that will happen very quickly.

Angelica [00:37:19] I think that was pretty much it. You have any other things you want to mention?

Justin [00:37:27] I don't think so. Thank you.

Angelica [00:37:30] Thank you so much.

Dr. Allard [00:37:31] No problem, this was fun.

Justin [00:37:32] For taking the time to help us out.

Dr. Allard [00:37:35] I wish I had researched it more.

Angelica [00:37:39] Sorry, but could you introduce yourself, and explain.

Dr. Allard [00:37:40] Oh!

Angelica [00:37:40] Oh, we should at least get that.

Dr. Allard [00:37:46] So my name is Patrick Allard. I'm an associate professor in the Institute for Society and Genetics and I'm both a geneticist and a toxicologist, and sort of mix the two fields together.

Angelica [00:38:00] Thank you. Oh, sorry, what were you saying?

Dr. Allard [00:38:01] Oh no, I was actually going to reopen that Agent Orange letter that I received, if my computer allows me to log in, but it doesn't, so I won't. What's going on? OK,

yeah well, lost my computer. But again, the bottom line is that from I remember that letter just spoke about like on the ground, just noticing that with several generations now since exposure and we're still seeing, there's still those anecdotal evidence in the field that you see these super high rates of birth defects and people are trying to figure out exactly how to approach this. That's it.

Angelica [00:38:49] Thank you so much, again.

Interview with Christina on her family experience with Agent Orange (2/26/20)

Justin [00:00:04] All right. Please introduce yourself.

Christina [00:00:07] My name is Christina. I am a junior at UCLA.

Justin [00:00:13] OK. And can you tell me what you know about Agent Orange?

Christina [00:00:23] From what I know, Agent Orange is a big, well, I know that it's how it's affected the community rather than like any specifics that happened on the other side of the war. I know how it's affected the chemical, still affect my family members in the community to this day, such as birth deformities and, as well as the emotional scarring. But people choose to avoid such topics and communication about it.

Justin [00:00:52] Can you elaborate a little more on what you mean by, like, they try to avoid the topic?

Christina [00:00:57] So for an example on that, when I went to visit my family in 2012 I believe, I ended up visiting my aunt's side of the family and I had an aunt once removed. Her name was Vy and she was born with many deformities, such as being mute. She really couldn't move on her own and her organs didn't work inside, so she couldn't process food on her own. So what she would have to do was she was fed soft foods and soups. The family tend to just keep her out. She wouldn't move. So she doesn't have one arm. She just lays out on the bed all day. And when I ask the family, how's she doing? Like, what's her condition? They are very Buddhist. So they just chose to respond to me in a way that basically masked the effects of Agent Orange by saying it was something to do with their past life, whether it's she's reached a new level so her body can't take it or it's a punishment. I don't really remember. But I believe it's the first one. And then it wasn't till about two years after that event, because I was 14 at the time when I was 16, I watched this documentary on the effects of Agent Orange and I made the connection between the two. But they didn't choose to tell me directly that it was an affect of Agent Orange.

Justin [00:02:24] Do you think that's the case for a lot of families in Vietnam?

Christina [00:02:29] I believe so, because a lot of families, even in America, that are currently in Vietnam, much as the people that are in the current space where they have been traumatized as such, they choose to push everything back, believing that if they thought about the past, it would injure them further or, it would hold them back from succeeding in the current day, with their money, with their family lives and everything.

Justin [00:03:00] And how has your family conceived the the personhood of your aunt?

Christina [00:03:15] My family. Conceived it in a way that, well, I don't really think they have they just have put it off and have excused it, masked it with religion rather than choosing to believe any of the realities of it. It's very much making excuses for the past and for their whereabouts and everything. They want to basically forget everything from that time period that they have been involved in. They refused to talk about the war in any conditions or circumstances. And whenever anyone brings it up, they actually get upset. Yeah. So I'm unable to ask them any questions about why do you think this is? And the only answer I'll ever get back, if any, would be religion based. And if it wouldn't be that, it'd be like it's rude to ask, you know.

Justin [00:04:14] Do you happen to know who most likely was exposed in in your family?

Christina [00:04:22] It was her father, my aunt's father.

Justin [00:04:25] OK. Was it was he a soldier?

Christina [00:04:29] I think he was just a farmer.

Justin [00:04:30] OK. And was was his farm sprayed?

Christina [00:04:37] Yeah.

Justin [00:04:37] OK.

Christina [00:04:40] I don't remember much about that side of the story. I do remember my, so my aunt that is related to her, her name's Hoang. So my aunt, Hoang, she told me about their family and how they were really poor growing up, that he just worked on a farm, it wasn't even theirs. And him remembering like one day these people came in and sprayed some things.

Justin [00:05:05] So they sprayed it like by like in-person?

Christina [00:05:10] No, sorry. Planes. But he remembers seeing some planes flying by and it started falling down and it wasn't his farm necessarily, this like, sorry not in the farm, but somewhere nearby on the farm. Yeah. So it was just close enough that he could see it.

Justin [00:05:27] Has he. Has he had any more kids?

Christina [00:05:30] He has one other child that for the most part is OK. It just ended up taking effect on the older one I believe. Yeah.

Justin [00:05:42] And in their experience and in your experience where they did. Did they receive a lot of support for having a disabled child but with with disabilities as extreme as that. And like one ones that are like seem to be caused by Agent Orange.

Christina [00:06:07] Because, from what I know their support mostly comes from my aunt and uncle that are living in America right now rather than from the Vietnamese government. They haven't been able to get support from the government because their other two children are well and they kind of think that it's just a genetic thing rather than a chemical thing. And I also believe that's why they choose to avoid saying it's part of the war, because that may be a little a lot more frustrated if they can't get that support from the government and it is part of the war. Other than that, I don't remember them saying anything else about support.

Justin [00:06:53] Who do you think is ultimately responsible or who? Who do you think should be responsible for Agent Orange? So so I guess a little context is that obviously when they began spraying, when the U.S. government began spraying Agent Orange, it was intended primarily as an herbicide and obviously to target crops as well, to starve out and reduce cover for the Viet Cong and with with the high rates of cancer and birth defects not being intended at all. So and it was only discovered later that impurities in Agent Orange, specifically dioxins, were like that's that's the toxic compound that's responsible for these detrimental effects in humans. So with that in mind, who do you think bears responsibility now?

Christina [00:07:52] I believe that both governments do bear the responsibility better than the civilians. I think that. What the U.S. government is giving right now for financial support isn't enough. And I also believe that they should provide the Vietnamese government more support in vetting through the people that need the health support. And the Vietnamese government should open a more. Like a less biased conversation towards it, rather than trying to mask everything up like everything's OK. I feel like the Viet government frequently does that actually where anything related to the war or anything related to Agent Orange shouldn't be talked about. It's a shame if you do, just focus on what's happening right now or they kind of scare you into not talking about it. I remember in the time that I visited Vietnam. You weren't allowed to talk about the war, you weren't allowed to look into a soldier's eyes when they would like drove by or

something like that. And that was only like that was less than 10 years ago and that stuff was still going on. And I think that the Viet government could do a lot better at making it a conversation if they choose to. That's the thing they're choosing not to, and the U.S. government isn't giving as much as I think they should as well.

Justin [00:09:11] Are you, do you know about the phenomenon of, I guess, ultrasound scans in Vietnam? Have you heard anything about them?

Christina [00:09:22] No.

Justin [00:09:24] OK, well, based based on our research, apparently women in Vietnam are particularly worried about their prenatal health. One for the purposes of sex selection, because Vietnam is still a very patriarchal culture and two like with this like backdrop of Agent Orange on their minds and with like this, an underlying fear of birth defects. Prenatal technology, specifically ultrasound scans have been very popular and widely utilized by women to ensure, in a sense, overused, because you only need to get an ultrasound scan once or twice during pregnancy, not up to 10 times as women do. And apparently Vietnam also has very high rates of abortion as a result of this, like the availability of this technology. So can you, can you speak to any of that in your experience?

Christina [00:10:41] In my experience, I'm unaware of anyone that actually does that or has. Yeah, I don't know of anyone in Vietnam that currently does that much. I know that if I'm thinking back, I know my aunt in law, on my mom's side, she immigrated from Vietnam to marry my uncle and I remember during her first pregnancy, she was very anxious. But, you know, it's a woman's first pregnancy, so I can't really put that on her to say that she experienced a fear of having a deformity in her child or anything like that. But the anxiety probably does come with one being a mother for the first time, but also probably seeing everyone around you because she grew up in Vietnam, experience that as well. But from my personal experience, I don't, I'm unaware of anyone going through it.

Justin [00:11:38] OK. OK. It. It seems to be that is it is something that is like like you said, like you sort of touched on like the culture in Vietnam. So there's like not talk about these. On the surface, talk about these harder topics and just sort of try and focus on what's good. That seems to be the dominant popular culture?

Christina [00:11:59] Yeah.

Justin [00:11:59] Okay.

Christina [00:12:01] Yeah. So I feel like a lot of the times, things such as frequent miscarriage, which my other aunt had a lot of miscarriages, she had three before she had her first child. And

the thought of like getting a like aborting a child or stuff like that. That stuff is glazed over. And even if it does happen, you mentioned it once, you cry about it and then you completely are forced in this culture to suppress it. It's something that I only remember them saying once as a kid and then growing up like, it's no longer a conversation in the household. Like remember the child you lost or remember like, when you went through this traumatic experience, they never talk about it. They never grow from it, because they never talk about it. You know, they're just kind of stuck in the time right before it and they skip over it.

Justin [00:13:15] How, can you speak to the importance of like family to identity in Vietnam, like how like how important is it to be able to like maybe especially for women to be able to bear children and like have a family to like your sense of worth, like your sense of personal and social worth?

Christina [00:13:42] As a Vietnam American woman. Although I was raised in, redneck Kansas. You know, like I grew up raised by my grandma, who was born and raised in Hanoi. One of the most traditional cities in Vietnam. So being raised by her. I had to live by the five traits of femininity from a young age, she would be like. These are the five traits and I don't know how to translate it to English, but it'd be things such as poise, posture, like being gentle like these types of traits that are stereotypically feminine and it's always the end goal is to start a family, to get a man, they really pushed it from a really young age. And I feel it was pretty damaging personally for my mental health and my self-confidence and self-worth as well. Where I just found myself thinking from an insanely young age like, does this guy like me? Like, Oh, like, that's how I'm successful like how, like, oh, I'm going to be smart so that like he'll pay attention to me, you know, like it just really changes your motivation to doing certain things and why you're doing certain things. You have to take a step back after growing up and learning to think on your own like. Am I doing this for a guy? Or am I doing this for myself? And what do I even want for myself? And it just changes your path of thought. And I feel like. This is just me growing up in America and experiencing second hand, but thinking about it being a culture that you're surrounded by. In Vietnam. A lot of women there and the men too these days, where they think, oh, I'm going to grow up to be this perfect individual to marry so I can make my way to the US. There's also that culture right now, too. It's been going on for a while.

Justin [00:15:42] OK. So, so assuming so let's so let's assume a woman who who is having her first child does give birth to a child with severe deformities that look like they may be associated with Agent Orange. How how do you think that would change her conception of like her her worth by and her social worth given, given the very family focused like importance given to women in particular?

Christina [00:16:18] It would easily mean in that culture that she's failed. It would be an immense sense of failure. She would think that something's wrong with her. She's been, on a

religious end a lot of them would believe that they had been punished by the gods like something that they've done wrong. It could potentially in some families mean shunning. And I don't know where else to take that because it's. That's how, that's sadly how straightforward it is, you know? Yeah, yeah.

Justin [00:16:58] And I guess. I guess the last question we would like to ask you is, do you think Agent Orange is a poison or do you or what do what do you even think a poison is or has that definition changed?

Christina [00:17:27] I think a poison is anything that can be a negative effect to one's body. So you know how people joke and they're like, oh, like like alcohol by definition is a poison to you. But people still consume it regularly to get this high, anything that gives you a high, any drug is a poison to you. So I think, yes, on a different level, in a different context. Agent Orange is a poison, even though it isn't meant to be. It wasn't meant to be at first, but it has the effects of a poison. And it's having the effects generations down and it should, it's something that needs to be treated. You need to find any solutions that you can. And if not, you can't if you can't find any solutions you need to treat the effects of it, meaning these deformities, give them good homes, give them medications to ease their pain. And the documentary that I watched there was a kid that somehow is still making it to the age of fifteen with a deformed heart, a heart that grew like outside a rib cage. And the family is not getting support from the government for that because they can't prove that they had been exposed to those chemicals, which is insanely messed up.

Justin [00:18:51] Is it, um, let me phrase this. Do you think a sort of like actual like a genetic or epigenetic test that could like very or more concretely establish, like, oh, yes, this is something that is caused or associated with Agent Orange. What do you think the implications of that would be? Something that establishes more of a biological certainty instead of a, because right now it seems to be that it's mostly anecdotal evidence. But if there was some way to establish more biological evidence that like, oh, yes, my child has these birth defects because of Agent Orange, what implications do you think that would have for the Vietnamese government,the American government, and so on?

Christina [00:19:55] While it would be a good thing for the citizens to be able to prove so that they could get treatment, I think that it could also be detrimental to how the citizens right now they're coping in their own way, which is denial, which is a stage to coping. Yes, but I feel like if all at once they were able to prove everything and point fingers. I feel like it have a negative impact because they haven't had a history of dealing with it healthily. For the U.S. and Vietnamese government, I feel like. They feel like they would finally have to own up to what, to the consequences of their war and everything, which would be very. It would be a hard path to tread down, but I think at the end it would hopefully lead to a resolution.

Justin [00:20:55] You you also pin blame in a way on the Vietnamese government too? Or responsibility, not blame, responsibility.

Christina [00:21:05] Responsibility, yes. Not necessarily, I don't pin blame on them for this. I pin responsibility because at the end of day, it is like they are their citizens. The citizens are being affected are theirs, and they should have more, take responsibility in pitching this to the US government at least for a more reasonable, more reasonable assistance, like more of a hand into it, rather than just nodding, taking, and then telling their people to shh, you know. I feel like what they're doing is very passive right now and it's not good for their people.

Justin [00:21:46] OK. OK. Thank you for your time. I think that's all the questions we have right now.

Christina [00:21:56] So, yeah, thank you.

Professor Matteo Pellegrini Interview

Rob [00:00:04] So if you don't mind to start, can you introduce yourself and the research you conduct here, specifically?

Professor Pellegrini [00:00:17] Yeah. So, I'm professor in molecular cell development and biology, and my lab does genomics and some bioinformatics. The main focus over the years has been the study of DNA methylation. To do that, we use a technique called bisulfite sequencing, which is sort of a variant on just standard DNA sequencing that lets us measure whether cytosines it seems in the genome or methylated or not. And that's where the DNA methylation term is referring to sort of the study of methyl cytosines. So where is it?

[00:00:55] How frequent is it at these positions? So over the years, we've you know, we've done many, many different studies. Initially, we were just kind of characterizing the distribution of methyl cytosines across genomes of different species. Then we sort of were able to, as sequencing technology improved, we were able to gather data across human populations and mouse populations and study sort of how the variation in DNA methylation was associated with different traits of interest, mostly metabolic traits. And more recently, we've sort of been developing kind of less expensive assays to do this so that we can profile larger populations. And the main traits we are focusing on nowadays are mostly related to aging. So people notice that you can correlate the methylation status of an individual with their age. And so essentially you can predict the age of individuals. And so you can couple this with aging-related research to see whether some people are aging more rapidly than others. Mean, whether the DNA methylation

pattern can tell you that. And then you can start to ask, you know, what factors influence these different aging rates across the population. Okay.

Rob [00:02:23] It's interesting that you've done DNA methylation research because there's been a lot of rodent studies with evidence of following that initial idea that it was an epigenetic mechanism. So there is kind of Princeville pathway that is TCT, at least in the animal studies they found binds to Aryl-Hydrolase. And through that, like one of those few ways that they've identified it affects the genome.

Rob [00:03:05] One of the main pathways it alters is typical DNA methylation patterns, but causal relationships on what the actual effect of that isn't a clear yet, but the methylation patterns have been associated with patterns of reproduction, altered sex ratios, like I said earlier, but it's mainly through the sperm carrying the genome. So that's also how it's inherited directly through the male lineage. So do you have anything to speak to on how an altered DNA methylation pattern would kind of affect reproduction?

Professor Pellegrini [00:03:57] Well, I mean, obviously, you know, human males are producing gametes, right? So the sperm and the sperm have methylation patterns and those could be affected by any kind of environmental factor. So it's clear that if you expose sperm to substances that alter the method that would be passed on to the next generation, it's not completely clear how you would get another generation because presumably, you know, the effects would dissipate. But I guess it's conceivable that it would persist longer than one generation.

Rob [00:04:39] So is it typically understood that like these changes can't really be passed on?

Professor Pellegrini [00:04:48] Generally, it's hard to pass. Yeah. I mean, you know, there's sort of the reason why most sort of heredity is based on genetics and not epigenetics. So obviously, you know, a pregnant woman has kind of three generations, there's the mother or the fetus and then the germline of the fetus, are all present at the same time, and so any environmental effect that changes the epigenome would affect all three of those generations. In a male, it would just be two generations. Right. The father and his gametes. It's possible that, you know, somehow you could extend it even further if there's some persistence of some factors that go wrong, but the DNA methylation profiles, persay tend to be reset during the formation of zygotes. So when the sperm and egg formed a zygote, there's a lot of epigenetic changes. And so the sort of waves of deep methylation and then re-methylation. So it's not like a terribly effective mechanism for passing information from gametes to zygotes. [00:05:59]But since it's certainly possible that some information process either directly through methylation or through some other factors RNA is or other factors that are passed on from the two gametes. [14.3s]

[00:06:15] So when we kind of initially stumbled upon the fact that every single time the epigenetic effects of TCDD are described, it is always connected to transgenerational effects. So, is that not usually seen in epigenetics?

Professor Pellegrini [00:06:48] I mean, well, like I said, I mean, you could certainly see one. You know, if you're going through, if you're affecting the male gametes, then that's going to pass on to the offspring.

[00:06:56] Now, whether it can pass on another generation through male gametes, that's harder because male gametes would be largely reset and epigenetically during development, but not completely. So, there's certainly some possibility. And like I said, that, with the female, if the female is exposed, then you would be potentially exposing also two further generations.

[00:07:22] So, you know, obviously there's interest in kind of how epigenetic information can be passed on. It's just very, very hard to study. And the mechanisms are not well understood. So that the sort of the general thought is that whatever information can persist would kind of decay rapidly because of the way the whole system is designed as to kind of reset the epigenome as the zygote develops into the different lineages, it's primarily resetting the epigenome and then reforming the different epigenome is associated with each cell type in your body. Right.

Rob [00:08:02] So it's there not a high extent of inheritance of the epigenome?

Professor Pellegrini [00:08:14] Right. Exactly right. So you obviously you completely inherit the genotype because that persists across multiple generations. But the epigenome is by and large reset because, you know, the gametes have a certain epigenome. Right. And then they fuse to form a zygote. Now the zygote itself then goes on to form all the cells in your body, which have very distinct separate genomes. So, in order to allow the zygote to, you know, prep for this big cellular differentiation, there's a lot of resetting of the epigenome. Specifically, in the case of DNA methylation, there is a large degree of removal of methyl cytosines from the epigenome in the zygote. And then it gets re-established in the gametes as they develop. And so there's a lot of studies which look at how rapidly the epigenome is erased and then reset in the male and female gametes. But because of that, yeah, it's sort of harder to identify mechanisms that permit the transfer of information across generations. [00:09:27]But, you know, I think there's also a lot of evidence that there is transfer. [5.7s] So, you know, there's other mechanisms you can imagine, not just DNA methylation, but also, you know, there's a lot of RNA, and other factors that could be passed on from the gametes to the zygote that then impact development. So, I think mechanisms that go from gamete to the zygote that you can come up with lots of plausible mechanisms. How you then go an extra generation is even harder. Unless, again, it's the mother who's been exposed because then you would have two.

[00:10:12] But that doesn't mean there is no effect beyond that. But it's just it's harder to identify specific mechanisms that persist beyond those immediate generation.

Rob [00:10:24] OK, so kind of based on that day, it was like I mentioned that through the Seveso, Italy Study-- that that's kind of where that idea of it being an epigenetic effect, started. And the most we could really find is the really huge deviation in reproductive patterns that we saw in infants and that generation led into that hypothesis, and that it was an endocrine-disruptor so. You have really speak to how the initial hypothesis of it being an epigenetic effect, is kind of established. It just seems that if that's not--if these transgenerational effects aren't that common--what's the case?

Professor Pellegrini [00:11:21] Well, again. There has. You have to be very specific about which generation you're talking about. Right. So obviously, when the explosion [in Seveso, Italy] happened, you're presumably exposed. Pregnant women

[00:11:30] And then that could affect two additional generations. And you exposed men who would then reproduce. And so that would expose one more generation through the paternal side. And then there could be a, you know, some additional presumably less strong mechanisms that persist beyond that. But it should be okay. I mean, at some point you shouldn't. If the mechanism--I mean, if the effect size is persisting at the same level across multiple generations, beyond the immediate ones, then you have to start to wonder if you know the sort of kind of genetic effects as well. All right.

Rob [00:12:11] So it's cancers like the third and fourth generations, kind of fresh ones unexposed that bring about the idea that it's transgenerational?

Professor Pellegrini [00:12:18] Yeah. I mean, through the mother you get first and second generation is after exposure--

Rob [00:12:26] Because they saw F1 & F2, but then saw F3 effects.

Professor Pellegrini [00:12:27] Yeah. At F3, now it gets harder.

[00:12:29] And what's the mechanism that persists in F3 that really requires that something, especially if you're saying this is mainly through the male, then that's harder to imagine how something you know is impacting the gametes of the F0, that then obviously could impact F1. But then how would it persist to F2 and F3? I think just our understanding of mechanisms that lead to that kind of persistence are not so well established.

[00:13:03] I mean, there are labs here at UCLA that studied these kinds of multi-generational effects. So it's entirely possible that we just don't understand that, you know, the system well

enough to know what could lead to such persistence. But most of the mechanisms we do understand should decay more rapidly than that.

Rob [00:13:21] So do you think it was probably by chance, that it is established as epigenetic?

Professor Pellegrini [00:13:30] Well, I mean, you can know, you can tell whether they're easy to assay for a genetic change, by sequencing the individuals.

Rob [00:13:45] So as long as you establish it is not genetic, that's enough to say that it's epigenetic?

Professor Pellegrini [00:13:45] Right. I mean, there's only two. You know, obviously a genetic effect would be harder, because you'd have to have a compound that's mutagen. And so, it mutagenizes DNA, and that typically leads to cancer. So, you might know, people are exposed to radiation or, you know, like Chornobyl or something that should show up as some kind of, you know, higher cancer rates that could potentially persist for long times. But, you know, if you're seeing specific defects that are more endocrine tumors and then maybe that goes against the genetic alteration, and then maybe there's some kind of compounds that for some reason keep disrupting these and different mechanisms across multiple generations. But yeah, I mean, this it's just very hard. You can try to do like epigenetic studies across these human populations, see if there's an effect, but probably hard to find.

Rob [00:15:04] And it's kind of backtracking, but it would be helpful to hear it from you because you're much more knowledgeable. It's kind of our initial exposure to epigenetics--how did you define the field and what are the main directions of research?

Professor Pellegrini [00:15:37] Yeah. I mean, so. So, you know, the main things. So obviously, genetics, we all understand you look for changes in the DNA sequence and then those would persist across generations. Epigenetics defines essentially the state of cells. [5.3s] Right.

[00:15:53]So all the cells in an individual have the same genome, but they have different phenotypic manifestations, different types of cells, neurons, blood cells, et cetera. The reason those cells are different, despite the fact that they have the same genome, is because they have different epigenomes. So, basically, the differences between the cells are what we loosely refer to as the epigenome. And they manifest themselves in different levels. Some are direct modifications of the DNA itself, like the example I gave you methyl cytosine. Some are modifications of the proteins that the DNA is wrapped around, so the nucleosomes--the DNA is not kind of free-floating in a cell. It's tightly wound all along proteins. And this affects, you know, the physical-chemical properties of the DNA. And so those proteins are bound. And how there are different from cell to cell defines the epigenome. [58.6s]

[00:16:53] And then you could go beyond that and say, you know, the current state of the cell, like, you know, which genes are being transcribed, how much they are. And so that could also be, in a sense, related to the epigenome. [8.9s] So sort of the downstream. But typically when we talk about epigenetics, we're mostly referring to the first two. So ,the direct modification of DNA and modifications to the proteins that the DNA is directly contacting.

Rob [00:17:20] So the principle pathway I'd mentioned early that TCDD acts--. So, I kind of caught what you mentioned. Can anything be directly modified by changing histone acetylation because of that?

Professor Pellegrini [00:17:37] No, no. They're two separate pathways. So, there's enzymes that can directly modify a CGT bases such as the ones you know, of which the DNA methyltransferases are the best studied and most prevalent. They add a methyl group to the cytosine. And that, by and large, persists for a long time because there aren't enzymes that can directly remove that. So it can persist. And then the DNA is wrapped around these nuclear bombs. The nucleosomes themselves aren't modified. So there's a lot of, you know, different patterns of methylation, so all kinds of modifications are occurring to the new systems. And so this term is called a histone code, which basically tries to define the particular state of each histone in each nucleus at each position in the genome. And that varies depending on, you know, whether the genome is active, repressed or what kind of a particular state of the genome.

Rob [00:18:35] So is that kind of reset as well?

Professor Pellegrini [00:18:37] Yeah, well that's reset even more so in terms of length scales, you know, as we said, the genotype by and large persists exactly across a generation. Right. The DNA methylation patterns are intimately tied with development. So, you know, as the zygote starts to differentiate along different lineages, you get a divergence of these DNA methylation patterns across the different lineages and they can continue to change as people age. That's why we use it as an aging primer. But that tends to happen slowly. I mean, fast at first because things are better and then more slowly. Later on, the nucleosomes are modified more rapidly. So ,they are more closely connected to sort of the transcription or regulation of a cell. And so, as cells turn genes on and off, the nucleosomes are typically altered. So that can change even more.

[00:19:35] And it's harder to do so in terms of what can persist across a generation. And obviously the DNA sequence can persist. The methylation patterns do get largely reset and reestablished. But again, some parts could persist. You know, you can imagine the nucleosome's, they also get completely changed and on a more rapid timescale. So. it's even harder to imagine--how nucleosome patterns could persist for longer. But again, it's not possible. It's just it gets progressively more difficult to come up with ways to do that or mechanisms for doing so.

Rob [00:20:17] Because we can't really do human research with TCDD, it's done with, principally, mice. Right. And interestingly, in zebrafish studies, those three they've been able to establish it is transgenerational, because there was F3 and unexposed generations, and all of them tracked histone acetylation and DNA methylation changes. How well did the animal studies transfer into human effects? So they're just everything that they're establishing in animal studies, they're saying there's strong belief that that's the same patterns in humans. How accurate is it to draw that relationship?

Professor Pellegrini [00:21:15] You know, I think these studies are extremely difficult and very often being controversial because, you know, in order to demonstrate this convincingly, you really have to control for all the other effects that could be leading to an F3 regeneration. So, you know, I think it's just hard to do this in a convincing and reproducible manner. And it's also very hard to find the mechanism that's leading to this persistence, even if you could convince yourselves it's affecting F3, and you're getting very similar results across different labs. To find the actual mechanism, whether it's an RNA that's persisting in these gametes across multiple generations, or whether it's a DNA methylation pattern that somehow isn't being fully reset across the generations or whether it's some nucleosome patterns, modifications that are persisting, you know, it gets very hard. [45.8s]

[00:22:19] [00:22:19]But if you could show that convincingly, then I think it's entirely plausible that the same mechanism would occur in humans at this time. At the basic biology level, there's essentially no difference between a human zebrafish or a mouse. So any mechanism that you identify that could explain this persistence in those species could very well translate to humans.

Rob [00:22:52] Ok, I have two questions left. So I'm not sure if this is even really something that is developing, but is there developing technology ,or the necessary resources to be able to identify this in humans? Because there's kind of two-sided problem of, obviously we can conduct human subject research with this compound just because even at low levels, like any of the effects we see here, very detrimental health. And in Vietnam, even if one can identify a generation that's believed to be directly affected by Agent Orange, they can't concretely say that. Are we just really far off from being able to trace these effects in humans?

Professor Pellegrini [00:23:54] It would be very hard because, as you said, I think one of the biggest confounding factors would be, is there some kind of environmental factor that's persisting? And not simply, you know, something that occurred initially and then went away, because like you said, these factors can, you know, often they're stable in the environment and can constantly affect generation either in Italy in Vietnam, right. So I'm not sure how you would go about excluding that. Obviously, you can do experiments in mice where you're controlled. But for human studies, it would be much harder. You'd have to find people who have, you know, an exposed generation that then moved away to a different environment where there's no affect, and

yet the effect persists. So you could conceivably do these studies and look at the epigenomes of their gametes across multiple generations and see it.

[00:24:46] But even just finding the initial effect on the gametes, the epigenetic effect on the gametes, I'm not sure that's been well-established either. Right. Those are not trivial experiments because as you heard characterizing the epigenome is very complex. Right. You have the full genome and you have to do the full methylome. You have to look for, you know, then all the histone modifications. And then, you know, there's sort of inherent variability in measurements and who knows how small an effect you're looking for, and then to show that that persists would not be trivial. Right. And so, and that effect might be a lot smaller than the effect from the environment, which maybe you can't completely get rid of in the experiment.

[00:25:31] So, yeah, I think in humans it would be super challenging unless you really tracked people who had moved away and then you started doing epigenetics on their gametes and see that there are some effects. But I've never seen any studies where they convincingly shown that the gamete epigenome is altered across multiple generations, even in animal studies. It's hard. I think a lot of it remains controversial because they're not easy studies to do. And although you try to account for all the confounders, small things that you don't think about, it might also be giving the facts.

Rob [00:26:18] And assuming that its models that have associated epigenetic effects with a lot of these diseases--if it were to be confirmed to be mediated by epigenetic effects, is there anything specifically dangerous about that over changes that would be inherited in the genome?

[00:26:57] So, is there anything specifically dangerous about epigenetic effects?

Professor Pellegrini [00:27:00] Well, in a way it's less dangerous, right? Because if it really is an empty mechanism, it should decay with time. Whereas if it's genetic, then that genotype could persist in the population for a long time. Unless it obviously has a big detriment on the survival of the progeny, then it would probably peter out as well. But no, I don't think it makes it more dangerous if it's epigenetic versus probably the opposite. Unless again there's a persistent environmental cause to the epigenome that's constant, then that could persist for a long time. I mean if my new levels of this compound in the environment continuously cause, you know, generation after generation, then we get to know that. Right. So, if you were to guess, that's the most likely hypothesis, because we have you know, we see epigenetic changes in the population over time due to many factors, very global factors or environmental factors. So it would be good to understand this.