RENE KAHN: Thank you very much for coming to the Grand Rounds, which will be given by someone from our own faculty-- not only someone, but a very special person from our own faculty, Dr. Rachel Yehuda, who's been here in this faculty for many, many years. She joined somewhere in the early '90s or late '80s. And she studied PTSD before you could even pronounce it and knew what it was.

She was one of the first researchers in the field of Post-Traumatic Stress Disorder. And actually, the first time we met, she asked me whether I would want to collaborate with her. And I was unwise and stupid enough to decline that. And since then, Rachel's career has risen to the stars. I'm not sure whether the two are correlated.

But anyway, she's been extremely successful in the field of PTSD and in stress, the study of the biology of stress in general, has published hundreds of papers, has been continuously funded by federal agencies such as the NIH, such as the Department of Defense, and the VA, where she, as you can see here-- yes, as you can see here-- she actually is head of the clinical operations within the psychiatry department. She's also vice chair for VA Affairs, and she was just elected a few months ago as a member of the National Academy of Medicine, which is highly prestigious, as you all know. And we now have as a department, I think, seven members of this illustrious organization or society, whatever you want to call it. So I'm very glad that Rachel is now going to present on one particular aspect of her many studies, one of the more controversial aspects of her studies, and certainly which made quite a few waves when it came out. So Rachel, thank you very much for presenting here.

RACHEL YEHUDA: Well, it's great to be here. I am going to talk about a topic that has gotten a lot of attention, particularly in the lay press, also the scientific world. And this is the question of whether we're affected by traumatic experiences that occur in previous generations. And it is controversial, but we'll talk about that.

If we're affected, how are we affected? Is it that we inherit memories of a parental trauma or a type of fear of the environment? Or maybe we inherit symptoms like nightmares, irritability, or depression that are characteristic of trauma survivors. And we would want to know whether the effects acquired prevent us from responding effectively to the environment, because these kinds of inheritances might be cause for concern. And when this information is discussed, there's a lot of concern about the potential negative impacts of what's called intergenerational trauma or ancestral trauma or historical trauma.

But it's equally possible that the effects of parental trauma can be beneficial. Maybe what we inherit is a keener threat detector to better visualize and respond to danger or coping strategies or other traits reflecting a positive outlook, the ones that allowed our parents to survive adversity. Maybe we get a righteous indignation or more humanity and empathy, a moral imperative towards social justice. I think this is absolutely a thing that you see among the offspring of trauma survivors. And of course, these are not mutually exclusive possibilities.

We're very concerned in this field about how you measure and interpret parental or ancestral trauma effects. Are there specific behaviors, phenotypes? Are there changes in blood chemistry, hormones, or epigenetic changes on the DNA?

And we're also concerned with the mechanism of how those changes may have gotten there. And additionally, what is the best way to understand or interpret some of the changes that we do observe? Because that's a whole different issue altogether.

So I'd like to have this conversation by talking about our work on the adult children of Holocaust survivors that we've actually studied over a generation. And I'm going to want to tell you a little bit how I became interested in this question, because it was never something I set out to do. It's kind of a question that found me quite accidentally.

I was actually interested in Holocaust survivors. And I was interested in Holocaust survivors because I was interested in the effects of trauma and PTSD. And as Rene said, I started my career in the late 1980s as a postdoc when PTSD was just starting to emerge as a diagnosis. And it was a controversial diagnosis.

I want to spend a second telling you about why PTSD was controversial. It was no less controversial than intergenerational trauma is now. The reason among many others that PTSD was controversial was because science didn't really have a paradigm for understanding long-term effects of stress. And what the diagnosis of PTSD was all about is the fact that an event experienced even as an adult even that was way in the past when the threat is no longer still present could continue to exert an effect.

What science had was fight or flight. Science had extensive studies on what happens when organisms are challenged, what parts of the brain, what fear circuits are activated, and the hormonal response that begins with sympathetic nervous system and culminates with the hypothalamic pituitary adrenal response feeding back to actually contain the stress response system. But all studies on this topic basically showed that within hours, most of the biologic circuits that are activated go back to normal.

And maybe we're left with a memory. We're somewhat wiser as a result of the experience. But that certainly didn't explain why people would say, hey, I'm not the same person I used to be or why they were affected decades later.

Now we now have a science that can help us understand that. And that is the science of epigenetics, which can explain how experience leads to alterations that are enduring and change the way that organisms respond to their environment. And how does that happen? Under the right circumstances and in the presence of the right enzymes, there are all sorts of changes that can occur in the nucleosome, on the DNA, on the histones, that really either facilitate transcription or impede transcription. And this is how events can some people say get under the skin. But this is how it is possible for an experience to really leave a more enduring trace.

Now, my point here isn't to explain how epigenetics works but to show you that these processes can be measured. But in applying epigenetics to psychiatry and certainly to clinical studies, we have some real challenges. The main challenge is that epigenetic marks that are relevant to how genes function are ideally measured in promoter regions of the genes in cells of organs of interest. And since nobody really thinks that PTSD or any psychiatric disorder is a disorder of the blood, it's very challenging to try to relate information that is mostly obtained from blood samples to the true processes that occur.

But one day, we can get there from here. And I think that it's really interesting to think about the field, how it evolved for a very long time in the absence of knowledge about epigenetics. How did the field conceptualize biologic changes occurring in response to trauma with just fight or flight, which everybody knew from the get-go wasn't going to be a sufficient explanation?

Well, the very first biologic study in PTSD was done by my mentors, John Mason and Earl Giller at Yale. And what they found in a very small study was that Vietnam veterans had lower urinary cortisol levels than veterans with other psychiatric groups. This was obviously a counter-intuitive finding, because stress is usually associated with increased cortisol levels.

And really, this wasn't a finding people paid much attention to. It was counter-intuitive. It wasn't really believed. And I would include myself in that group when I came to do my postdoc at Yale. I couldn't understand the finding and thought I would try to replicate it and was actually quite surprised when I, too, found that in combat Vietnam veterans, cortisol levels were lower.

So before struggling with what that might mean since it was kind of a very big paradigm changer if it were indeed associated with stress, low cortisol, we thought it would be important to try to replicate the low cortisol finding in other traumatized populations. And I immediately thought about the Holocaust, especially since I had remembered Holocaust survivors growing up not in the same way that the Vietnam veterans were presenting as very fragile with multiple problems. But as my mentor, Earl Giller, said, it was a testable hypothesis.

So we did an initial study. And lo and behold, cortisol levels were lower in Holocaust survivors with PTSD, very similar findings to what we had found in combat Vietnam veterans. And this, of course, really began a journey into trying to understand why cortisol levels were lower in PTSD. Now, imagine that this is 1991, because that's what year it was. And we have this finding of low cortisol without a real ability to get inside the nucleus of the cell and examine molecular effects.

But what we did know even then was probably glucocorticoid receptors were involved in explaining this finding. And over the years, we took little steps until a few years ago when we were able to publish this finding of lower methylation of the glucocorticoid receptor gene in peripheral blood of veterans with PTSD in association with PTSD. So it took about 25 years to go from the initial observation of low cortisol to the epigenetic explanation for how that could occur.

But I'm not going to take you on that 25-year journey. Rather, I started telling you a different story of how I got interested in offspring and it's because the Holocaust survivors were so very interesting. When we talked to them, we realized that even 45 years after the war, a great number of them still met criteria for PTSD. But almost none of them had ever been treated in psychiatry for mental health symptoms. And so it became really important to me to be able to open a clinical program for Holocaust survivors, which we did in 1993.

We opened up a clinic, which I thought everybody would run to if they were a Holocaust survivor because we were offering such fantastic treatment at such low prices, which basically was for free. But although some Holocaust survivors did call for treatment, the overwhelming number of calls that we got once we advertised our program was from offspring of Holocaust survivors, who self-identified for treatment. So we asked them, what brings you to treatment?

I guess we could have said this program is just for your parents. But really, so many calls, we couldn't really do that. And the offspring basically gave very uniform answers. They felt guilty, damaged, anxious. They've had morbid grief. They had intrusions of Holocaust-related imagery, problems separating from or confronting parents. Many felt the burden of compensating for past losses or messed up interpersonal relationships.

And what's really interesting about this list of problems is they're not the classic symptoms that people express. I'm feeling depressed. I can't sleep. They had those things too, but that's not what was urgently on their mind to tell us. And most attributed their problems to the Holocaust or at least being raised by Holocaust survivors.

They said damaged people raised me. My house was a cemetery with no joy or laughter. And my favorite, "we lived waiting for the other shoe to drop." And sometimes everything was fine, but there was just this sense that it could all be snatched away in an instant.

So it is in the early '90s. I'm at a very early time in my training. And not only that, my PhD is neuroscience. And so I had very little clinical experience. And it was challenging enough to try to figure out how to treat trauma survivors in the early '90s with PTSD let alone figure out what the treatment is for the clinical complaints that were associated with the second generation.

So we consulted the literature. And at the time, the academic literature, shockingly, disputed what they called the "myth" of damage to the second generation. And I have this little blue asterisk to remind me to tell you that that literature was largely written by adult children of Holocaust survivors themselves.

And the general tenor of that literature was that survivors are resilient. Their offspring are successful. Holocaust survivors survived against all odds. There was a tremendous reluctance to stigmatize or to acknowledge that there was an intergenerational effect. Although there was clinical and anecdotal evidence of psychopathology, those were considered outlying cases that didn't prove the generality that everything was OK.

Now, there were numerous descriptions in the literature and art that really seemed at variance with this. And to be honest, I was a little unsure what was going on. And I thought, what's missing from this conversation is objective scientific and biologic data that could help us put all of this in context. And that's how you think when you're in your early 20s-- late 20s, actually-- think that biology will really provide every answer.

But we did set up a research program that was designed to answer what I think are relatively straightforward questions. And although we've done many, many studies, I think that they can all fall into these three general questions. The first, do Holocaust offspring have more mental health problems?

The second, do they show biologic alterations that reflect trauma exposure? And if so, what explains these effects? And there could be a big range of explanations here, ranging from parenting effects, genetic predisposition, epigenetic accommodation, though we didn't know about epigenetics then.

So let's see what the answers to these questions are. The first thing that we did examined lifetime prevalence of PTSD, mood, anxiety, and found that it was higher in Holocaust offspring. And the increased prevalence of PTSD was not associated with more adult trauma, in fact, a little less. So it was very surprising. The finding was published in the *American Journal of Psychiatry.* But a colleague of mine was very upset by this paper and told me, pointed out, that it was a terrible study and not very epidemiologically valid because we had recruited a lot of people that had come to our program for treatment.

So I looked up the word epidemiology. And I found that it was true, that we needed to do this in a much more rigorous way. This had been a convenient sample.

I'm making a joke about it because I know that there a lot of trainees in the audience. And it's very important not to get flustered when somebody throws something at you that you've never heard of before. You just learn about it, and you incorporate it in.

We did an epidemiologically-valid study by getting a list of Holocaust survivors from the Cleveland Historical Society and then asking if we could interview them and their children. And it was completely a non-treatment seeking sample. What we learned from that study was that we only saw PTSD in Holocaust offspring if they had a parent with PTSD. And we did that by direct interview of both.

We realized that if we were going to continue to study Holocaust offspring, we wouldn't always have the parent. And this was an important variable. So we developed a questionnaire that we validated. We had a self-report part where the offspring filled out questions about the parent. We had interviews of the parent by a clinical psychologist.

And you could see this incredible concordance. And to me, that's a great story right then and there. How can you be so-- it really suggests a very tight lack of separation between what the Holocaust offspring knows and what the parent is feeling. But for the rest of the studies that I'm going to talk about, I want you to know that the parental PTSD is generally made by the offspring's assessment.

When we started to do more studies to try to replicate the finding, we learned that it is, in fact, the case that parental PTSD seems to account for most of offspring psychopathology, particularly PTSD. So the importance of parental PTSD, Holocaust offspring were more likely to have PTSD, depression, and anxiety if they had a parent with PTSD. And many of the mental health effects seem to be a consequence of parental symptoms, not parental exposure.

And I'm telling you this also because Holocaust offspring showed neuroendocrine and molecular changes, including epigenetic alterations of the glucocorticoid receptor, according to parental PTSD. So now I'll show you just a select number of biologic studies. Our lab concentrated on endocrinology.

We had very good reasons to do so. We had a unique endocrine signature in PTSD. And our grant funding from the NIMH was really designed to ask the question of whether these biologic alterations associated with PTSD could be seen in what we were calling a high-risk sample, that is, people who are more predisposed to developing PTSD. That's how we framed it.

So in the first study, we found that urinary cortisol was lower in offspring who had had their own PTSD but also a little bit lower, significantly lower, in adult offspring that had never had their PTSD but had a parent with PTSD. And then we systematically applied all the biologic tests that we had developed for the study of PTSD in parents or in combat veterans or in other populations to offspring. And I'll show you some of these.

Parental PTSD here is associated with cortisol circadian rhythm changes in Holocaust survivors that never had PTSD. That paper was published in the *Archives of General Psychiatry.* I don't have time to go into the exact circadian rhythm changes. But you can read about it if you like.

We used the dexamethasone suppression test, which has been a very well-replicated finding in PTSD that people show an exaggerated cortisol suppression to dexamethasone. And here, you can see that offspring of Holocaust survivors with PTSD also showed an enhanced cortisol suppression following dexamethasone and on and on. So Holocaust offspring with parental PTSD demonstrated similar endocrine alterations to those seen in PTSD.

So how do you interpret this? I never used the words intergenerational transmission. I knew that people were using those words. But to me, that seemed a little flaky. Like, what does that even mean? It's the way sometimes people say consciousness right now.

Well, we'll get there. But we don't study things that we don't really know how to study or don't have the mechanisms for studying. What I preferred was framing this in the context of PTSD risk or even offspring experience. And this is a study we published in 2001 that made a very big impression on me.

We administered the childhood trauma questionnaire to comparison subjects, Jewish offspring with no parental PTSD, offspring with one parent with PTSD, and offspring with two parents with PTSD. And while the groups do not differ in sexual abuse, physical neglect, or physical abuse, there are whopping differences with respect to emotional neglect and emotional abuse. And at the time, in the endocrine field, we were just learning that low cortisol might be a function of early childhood abuse.

And what I just figured was, I'm learning that low that low cortisol also applies to emotional abuse or emotional neglect. That's also an abuse, even though you can't really call child services when people would say to you, hey, you would have never survived the Holocaust or other such phrases which were constituting the emotional abuse that we were seeing. Well, I was totally wrong about this I learned after 9/11.

After 9/11, Mount Sinai was very interested in protecting all people who were exposed from environmental hazards. We still have the World Trade Center Program here today. But I got a call about a group of women Mount Sinai was following who had all been pregnant in the vicinity of 9/11 and who are being monitored during their pregnancies. And a lot of these women seemed to have PTSD.

So we were able to study these women. We were able to obtain salivary cortisol levels from women and their babies at the seven-month wellness visit. And what we learned was that mothers who had PTSD had lower cortisol levels than mothers who didn't have PTSD-- nice to always replicate this-- but that their seven-month-old babies also had lower cortisol levels if the mother had PTSD. And what was really fascinating about that finding was that there was a trimester effect such that the difference was most pronounced in mothers who'd been exposed in the third trimester. And I will come back to explaining why that would be so.

But for now, what I want to tell you is that this completely changed the way I had been thinking about the work. It clearly wasn't just about risk for PTSD, and it clearly wasn't just about early childhood effects. It started earlier.

And I started to wonder that with this whole time, we had not been separating out maternal and paternal effects. On the contrary, we were trying to recruit Holocaust offspring with two Holocaust survivor parents. But we went back to some of our data, and we had the information about whether mothers and fathers had PTSD. And with respect to the data on prevalence of psychiatric disorder, what you can clearly see here-- and this is a very large sample that I somehow don't have the ends here.

You can see that the prevalence of PTSD only went according to whether the mother had PTSD. But the prevalence of depression and anxiety in Holocaust offspring was not dependent on either maternal or paternal PTSD but rather on their exposure. So we developed a bunch of new studies that would change the paradigm and start looking at differences between mothers and fathers.

And so when we repeated the endocrine findings, we found that hiding in plain sight was a very big gender difference, or sex difference. And here, what you're looking at is a group of Holocaust offspring and controls divided according to, in the red, whether the mother has PTSD, mother or both parents have PTSD, or whether just the father only has PTSD compared to if no one has PTSD. And what you can clearly see is, with respect to this happens to be glucocorticoid sensitivity, the findings go in different directions.

There seems to be evidence of glucocorticoid sensitivity associated with maternal PTSD in the offspring, but just the opposite, which is more associated with depression, in the offspring of fathers. And we did this for lots of different tests. This is the DST. So let me add to this slide by showing that it's not only parental PTSD that's important. There are different patterns of findings in association with maternal and paternal PTSD.

All right, what explains sex-specific effects of parental exposure or PTSD? This is my little joke. "If they ask you anything you don't know, just say it's due to epigenetics." But in this case, it's true. And it's generally good career advice these days.

So there are a lot of candidate mechanisms for sex-specific intergenerational effects that have been shown to be underpinned by epigenetic mechanisms in animal models. So certainly, these include childhood experiences of maternal behavior, in utero effects, and effects of trauma on gametes like oocytes and sperm. And the question became, can we apply epigenetics to the study of these putative mechanisms inhuman offspring cross-sectionally without a developmental perspective?

And we decided to try. So first, we thought to examine the contribution of childhood experience of maternal behavior. And we based this on the very well-known work of Dr. Michael Meaney, who was a collaborator who had beautifully shown that glucocorticoid programming was associated with changes in the hippocampal GR gene methylation and that maternal behavior itself regulates epigenetic and HPA access changes in the offspring, though the mother herself does not have these changes. Only the offspring does.

So Michael had already worked out where the important transcription factors would be and what region to look at. And we developed primers that would allow us to look in the lymphocyte. And these are the results. We published it a few years ago now. But it's the first study showing epigenetic changes in association with parental trauma. And here, you could see the slides recapitulate the neuroendocrine slides beautifully, that there is a different maternal effect and a different paternal effect that follows closely with the endocrinology when you do this work.

All right, well, what about in utero effects? So I alluded to the in utero effects when I showed you the 9/11 studies. And I can just show you this nice slide. One of the things that's very obvious when you study-- I can't work this. That's OK.

One of the things that is very obvious and one of the main things that they learned from the Dutch Hunger Winter studies about the effects of starvation of mothers who are pregnant and the long-lasting implications is that when a mother is exposed while pregnant, she not only affects her fetus, but she affects her fetus' gametes. And therefore, an exposure that occurs during pregnancy could be expected to last for a couple of generations. Now, that makes perfect sense.

But why, then, is trimester important? And what if the parent is exposed to trauma well before conception or pregnancy? And how do fathers fit into this kind of a scheme, if they do at all?

So the first question with trimester is the easiest one to answer. Starting at the end of the second trimester heading into the third trimester, there are enzymes that begin to be expressed in the placenta whose function is to break down active cortisol into its inactive metabolite, cortisone. And the most well-known of these is 11-beta-hydroxysteroid dehydrogenase type 2.

And some people have described it as kind of like a placental shield. So cortisol is in the mother. It doesn't all get into the fetus, and we don't want it to because glucocorticoid for a developing brain may not be such a good thing.

All right, however, under some conditions, the enzyme may already be altered in the mother. And then it's a whole different ballgame. So under what such conditions would that occur?

So in parallel, we're doing this PTSD work in survivors in parallel with our offspring where we're trying to stay a step ahead in our regular PTSD work. But one of the things that you saw on the slide before was cortisol metabolism. We're very interested in cortisol metabolism in general in all PTSD. But in the case of Holocaust survivors, it seemed particularly important for us to account for effects of starvation, because that was a very major trauma that has very long-lasting physiologic consequences in offspring.

So what happens when you're starving, prolonged starvation, is that the same enzyme, 11-beta-hydroxysteroid dehydrogenase type 2, and other cortisol metabolic enzymes work together to kind of not work as well so that it can prolong local intracellular effects and promote metabolic fuel production and help sodium retention in the kidney. So when you're starving, you want whatever you get to last a long time. And having a lot of glucocorticoid is helpful in this process. So you want it in starvation, not in brain development.

When we looked at this in offspring, we found really that the finding went in a very different direction. This is the work of Dr. Bierer. When we parsed it out even more, we saw that it was the adult children of mothers who were starved in childhood that had this effect, which is kind of an accommodation effect. It was the younger people who were starving during World War II whose enzyme didn't recalibrate, didn't return to normal, as a result of glucocorticoid programming.

So what am I actually saying here? Well, imagine if, for whatever reason, there is decreased maternal 11-beta-HSD 2 because the enzyme never came back from where it was after it was developmentally programmed. This would result in an increased free cortisol in maternal placental circulation. And the adaptation to this on the part of the fetus would be an increase in 11-beta-HSD 2.

You see this in the babies born to women following the Dutch Hunger also. It's classic adaptation. So is this an epigenetic transmission? Well, it's very nuanced.

What I'm saying is that an effect that occurs prior to pregnancy can impact the pregnancy. It's not transmission, per se. But there is an adaptation that affects the fetus in a very enduring and permanent way. I think this is the beginning of our understanding of resilience, because it's not a passive transmission. It's an accommodation that is positive, that is meant to preserve something important in the fetus.

So now we move to effects of trauma on gametes. OK, and this is really hard, because we're just not measuring this in humans. So it's off the table. Although we have been collecting sperm from combat veterans, but we can't really do the kind of studies in people that we can do in animals. But what can we learn anyway, if anything?

I want to put up the consensus definition of epigenetics. If you put epigenetics in Google, this is the definition, you're going to get. It's a definition that was done at a consensus conference. I'm sure they agonized over every word. The definition says, "an epigenetic mark is a stably heritable phenotype resulting in changes in a chromosome without alterations in the DNA sequence." Isn't that a great definition?

Most people read that definition and they think heritable. I knew that it got transferred to your children. But that's not what it means here, is it? It's referring to mitosis, the word heritable here. It's referring to the idea that there is a stable phenotype from when the cell divides, when the parent cell becomes two daughter cells. Mitosis is designed to create carbon copies of cells to replenish the cells that we already have.

Can you apply this to meiosis? Yeah, sure, if for whatever reason the chemical changes occurring as a result of trauma exposure are occurring during any process of meiosis. Yeah, it's possible for there to be an epigenetic effect that is resulting from trauma. But again, meiosis is different than mitosis.

Meiosis is designed to create diversity among different sex cells. And also, there's a real opportunity for diversity in male and female responses, mothers and fathers. Because in females, females are born with all of their primary oocytes, which complete meiosis beginning at puberty one egg at a time whereas sperm is made throughout reproductive life in males.

So there are some implications of changes in gametes. When something happens to the parent may have implications for the offspring. And in females, early puberty effects on oocytes may be more likely to be represented or at least represented differently in offspring.

So I'm going to show you one more thing. This is the study that I think did, for lack of a better word, go viral. It got picked up by a lot of news and interpreted in many ways not correctly or in an exaggerated way. But it is a very interesting study.

We looked at methylation of the FKBP5 5G. What is the FKBP5 gene? It's a stress-related gene that works very closely with the glucocorticoid receptor. The glucocorticoid receptor, we were always going to measure because all of our work has focused around glucocorticoid receptor responsiveness. So this is a candidate approach. But the FKBP5 gene came from the very first gene expression study in PTSD, which incidentally we did here in collaboration with Joseph Buxbaum.

And FKBP5 was found from that hypothesis testing approach, two probes of FKBP5. So we tested that this gene has been implicated in stress responses and even genetic basis, genetic-environmental interactions of stress, contributing to depression, anxiety, and PTSD. And what we found was when we measured it in Holocaust survivors and their own children was this significant effect of FKBP5 methylation.

Now, what it looks like here is that Holocaust survivors' first generation had increased FKBP5 methylation, which is consistent with lower FKBP5 gene expression, which is what we reported. But the offspring had lower FKBP5 methylation. They're not opposite findings. The control groups also are opposite. This is a highly age-dependent effect, so these are the age-dependent. These are the age-matched controls.

But the actual FKBP5 methylation is correlated in parents and offspring. So one of the major criticisms of the study was that it was too small. It was too small. We weren't able to collect so many parent-offspring pairs. This was it. But we recently were able to replicate this study just in offspring.

We were able to have a much larger sample of 156. We're currently in hopefully the final stages of getting this accepted for publication. And because it was a bigger sample, we could look at variables that might be associated with FKBP5 methylation. And we found a lot of interesting things.

First, this definitely seems to be kind of a maternal affect on the one hand. But when you really look closely, FKBP5 methylation is particularly associated with maternal exposure in childhood in the opposite direction than it is in mothers more generally. It's complicated-- a lot of different stories in a sample of Holocaust offspring because there's a lot of different considerations. What's going on with parents? What's going on with the offspring?

But it raises the possibility that an effect in oocytes may be present that may then influence in utero events. Well, obviously, this can only be followed up in animal studies. But there's a reason to really think about maybe doing that. What was really interesting, though, is that anxiety disorders were more common in the children of survivors exposed as adults, not young children. So maybe this is the beginning of understanding a little bit about what protects people from the development of anxiety disorders.

Now, fathers are important to intergenerationally-transmitted effects. Adult male rodents show epigenetic effects in brain and sperm following fear conditioning that persist in the second and third generation. Sperm is made throughout reproductive life, providing a mechanism for transmission of adult effects, but also providing an ability for therapy to eradicate those effects in new sperm. And that has also been shown recently in animal models.

But sperm effects are manifest through changes in the placenta. So even when an effect is based on the father's exposure, the mother is always contributing. The mother is always involved. Now, obviously, we're taking this genome-wide. We have just looked at gene expression profiles in offspring. And it recapitulates distinct parental gender effects and has been submitted for publication. Nikos Daskalakis wrote this up. And what this is telling you is essentially that there are opposite effects in multiple genes and multiple pathways in association with maternal and paternal PTSD. And you can account for different variables, the genes that are associated with exposure versus the childhood trauma of the offspring versus maternal age and all of those things. So we hope that as this work develops, things will become clearer.

I'd like to spend the next minute or two wrapping up and telling you how I think we should interpret these findings. So what I've shown you is that there are two aspects of the intergenerational response that may work in highly different ways through different mechanisms and exert completely different influences. And that's just two variables. There are likely to be 10 or 20. But the two that I've talked about are parental PTSD. And even that doesn't work uniformly, because maternal and paternal differences are different, and age of exposure, and even that doesn't work uniformly, because it's going to be different in males and females.

Parental PTSD is linked with neuroendocrine alterations in psychopathology with different patterns for maternal and paternal effects. But maternal age of exposure may be a special window of opportunity for epigenetic effects that might reflect accommodations or resilience. Certainly, it might affect in utero environment. Certainly, it might then also affect stress during pregnancy and also maternal behavior. It's all really connected in very complicated ways.

Now, we've not provided an answer to how epigenetic changes in offspring got there. So I really want to be clear about that. And one of the things about why this work is controversial as Dr. Kahn said in the introduction is-- the data are not controversial. The data are the data. Nothing that you saw here is rocket science in terms of measurement, right? It's all pretty straightforward stuff. It's not even computational magic. It's just real data, right? But what's controversial is when we start ascribing a lot of mechanisms, when we start using words like heritable trauma, or trauma changes my DNA, and stuff like that, then all of a sudden, there's a lot for people to react to.

What we have done, I think, in our work is identify many potential opportunities for transmission to offspring that need to be followed up-- effect of trauma in gametes, intrauterine environment, stress during pregnancy, early maternal behavior. These things matter. These things are important, and they probably interact in ways that are also very important.

So my last slide is really, how should we interpret intergenerational effects? And I've given this topic a lot of thought. What any biologist will tell you is that epigenetics provides a mechanism for improving responses to environmental conditions, for improving responses to adversity. In biology, we don't think trauma is never going to happen. And if it does, oh, no, and it's all bad and pathological.

To the extent that we are capable of making minor changes within one generation that change the way we respond to adversity, that's, generally speaking, a positive. Sometimes it may be an impossible situation where you have to choose between two unpleasant options, and you do have a negative effect. But the real question about epigenetics becomes, are offspring living under the same conditions as the parent that may have transmitted something to benefit them?

And starvation comes to mind. I mean, if a parent is preparing a child for starvation and they live in this country at this time when the bigger problem is that food is too abundant, that's going to be a mismatch. Whether or not epigenetic improves or not is very context-dependent. And I speak to a lot of clinical audiences of people that don't understand the biology at all. But this they understand when I tell them that they should view epigenetics like through this example.

A mother gives her 8-year-old child a knife, a very sharp knife. Is that a good gift or a bad gift? Well, if the mother gives the child the knife right before she disappears and leaves the child hiding in the forest and tries to make sure that this child won't be caught by the Nazis and the child might need to use the knife in self-defense, that is a very good gift. But giving a regular child that just lives in the Upper West Side a very sharp knife, the child might hurt him or herself.

When the child grows up, knives are kind of neutral. They can be used for cutting food. A knife might inspire someone to become a surgeon. So the epigenetic marks themselves, you can't view them with meaning yet, right? That's something that we have to take a lot of factors into consideration for.

But the fact that there is an accommodation means that we're not prisoners of our genes. And the capability of transformation, I think, promotes resilience, flexibility, and plasticity. It's not that we want to get rid of the epigenetic effects. We want to have better environments so that we can promote the right kind of adaptations. So epigenetic marks might be looked at as weapons of mass construction but also a double-edged sword.

I really want to thank my team at the Bronx VA. And particularly, I showed you the work of Dr. Linda Bierer and Dr. Amy Lehrner, Dr. Janine Flory takes care of all of our diagnostic work. Heather Bader, Iouri Makotkine runs the lab. Nikos Daskalakis is a postdoc, did a lot of the molecular work and Frank Desarnaud, Julia Golier, and others here. So thanks very much for your attention.

[APPLAUSE]