Anna Rascouët-Paz: Hello, and welcome to Annual Reviews Audio, part of the Conversation Series from Annual Reviews, where insightful research begins. I’m your host, Anna Rascouët-Paz. In each episode of our show, we speak to top scientists in fields ranging from astrophysics to sociology. Today, we are talking to Suzanne Fenton, the leader of the Reproductive Endocrinology Group of the National Toxicology Program at the National Institute of Environmental Health Sciences. She and her team study how early life exposures to environmental chemicals affect breast development as it relates to the timing of puberty. Working with rodent models, they are attempting to determine the underlying mechanisms of the resulting susceptibility to breast cancer, as well as the consequences for the ability to lactate. Professor Fenton is the corecipient of the 2008 Level I Scientific and Technological Achievement Award, a top honor from the US Environmental Protection Agency. Professor Fenton, welcome to our show.

Suzanne Fenton: Thank you.
Anna Rascouët-Paz: You are an author of an article, published in the 2012 Annual Review of Pharmacology and Toxicology, titled Perinatal Environmental Exposures Affect Mammary Gland Development, Function, and Cancer Risk in Adulthood, which you cowrote with Casey Reed and Retha Newbold. Let's start from the beginning. What can you tell us about the stages of puberty in girls, and whether those stages are regulated in the same fashion?

Suzanne Fenton: A lot of people may say there are three or four stages. In my opinion, there are about three. They are thelarche, which is the appearance of breast buds—when the breasts start to develop to where you can see them; pubarche, which is the development of pubic hair and auxiliary hair on the body, whether or not the girl wants it; and then menses, the first period, and there would be regular cycles after that. These do appear to be regulated differently. The timing may vary between the different stages of puberty, and therefore environment may impact each separately.

Anna Rascouët-Paz: What is considered early puberty?

Suzanne Fenton: That may vary, again, by the scientists who are working in that area. Most agree that it is the appearance of breast buds before the age of eight—some say the age of seven. Sometimes this may be controlled by abnormalities in the brain, but many times we don’t know the underlying reason for either early or delayed puberty in children.

Anna Rascouët-Paz: It’s understood that early puberty or even delayed puberty—breast development, more specifically—is a problem. What is the issue there?

Suzanne Fenton: There can be a lot of problems with early breast development and early puberty in general. Some of the reasons are psychosocial; you’re not the same as your friends. It’s really hard for eight-year-old girls to understand how to deal with having a period or the development of breasts.

Another reason is it may enhance early promiscuity and may increase the number of people who are having babies who are under the age of 16, for example. But the reason that we really focus on, in my lab and in my research, is the risk for later-life disease. Specifically, it may have effects on lactation or on breast cancer risk in later life.

Anna Rascouët-Paz: Which are the populations most affected by this issue?

Suzanne Fenton: In the United States, it’s been given a lot of attention, but this is not the only place where there is seemingly a problem. The Danish National Birth Cohort has published more than one article now demonstrating that children in Denmark, and in some of the [other] northern European countries, also have early pubertal signs; specifically, breast development is occurring earlier there then it did two generations ago.

In fact, in one of the most recent articles from them, they looked at breast developmental timing 15 years apart, and in only 15 years they saw a significant trend for earlier breast development over that time. It’s very striking. It certainly can’t be because of a shift in genes or heredity.

Anna Rascouët-Paz: It sounds really quick. Has this effect also happened for the age at which girls get their period?
**Suzanne Fenton:** That does not appear to be as affected. There have been small changes noted in that, over longer periods of time, but the timing of menarche does not seem to be as affected as breast developmental timing.

**Anna Rascouët-Paz:** Focusing on breast developmental timing, what could be the potential causes of early or even delayed development?

**Suzanne Fenton:** Most of our studies are in rodent models of human disease. In our rat and mouse studies, we have shown that several chemicals can affect mammary gland developmental timing. Those would be atrazine and its metabolites; PFOA (perfluorooctanoic acid), which is a surfactant that’s used widely for things that are grease proof or stain proof; flame retardant mixtures; nonylphenol, which is found in plastic; and dioxin, which is a common pollutant. These are the chemicals that we’ve actually seen shift mammary developmental timing. Some cause early developmental timing, and some delay the development.

**Anna Rascouët-Paz:** How do they act, exactly?

**Suzanne Fenton:** That is the million dollar question. We know how they don’t act, some of them, and for most of them, we don’t have any idea how they control mammary gland development. One of the things that some of them have in common—for example, atrazine, PFOA, and dioxin all delay mammary gland development. One of the things that they do is cause the branching patterns in the gland to be delayed and stunted. We think that the mechanisms may lie there, but we’ve tested only a few chemicals, and there are potentially 86,000 or so chemicals on the US market.

One of the major problems is that some of the testing that’s done does not actually evaluate mammary glands as an end point. Even though [tests] may look at pubertal timing in a rodent model, they don’t usually look at mammary gland development. We need to enhance our ability to evaluate the mammary gland in order to catch up and determine those mechanisms.

**Anna Rascouët-Paz:** You’ve talked a little bit about delayed breast development. How is this a problem, exactly?

**Suzanne Fenton:** That’s an interesting question because you would think that if you delayed breast development, it wouldn’t be a big deal. But what’s happening in girls today is that they may start breast development early in their lifetime, but it isn’t completed until they undergo full sexual maturation, which includes having their first period and cycling normally; the timing of that isn’t changing. What’s happened is that there’s a longer window of time in which girls’ breasts are developing.

We know in rodent models that the longer the sensitive structures called the terminal end buds are present in the mammary gland, the more sensitive the gland is to a carcinogen. Potentially, if that translates to women or girls, then girls who start breast development earlier would have a longer window of time in which they were sensitive to the effects of any other environmental contaminants, especially carcinogens.

**Anna Rascouët-Paz:** One of the sections in the review discusses fat cells, and people talk a lot about dealing with obesity. How do these two things interact?
**Suzanne Fenton:** Some of the more recent publications on why we have this precocious puberty epidemic suggest that it may be linked to the obesity epidemic. In my mind, those may actually be linked with environmental causes. The breast is made up of a lot of fat, and the epithelial cells where cancer is formed are layered and nestled within that fat. The fat cells actually produce hormones that can affect the cells that form the adult breast, form lactation units, and form cancer. There’s an interaction between the cell types within the gland, and the fat cells are more numerous in girls who are obese. They’re larger cells, and there may be more cells; we know environmental chemicals can actually cause obesity in rodent models in the lab.

We also know that some of these same chemicals can alter pubertal timing, but what we don’t understand very well is whether or not the cart is before the horse, or vice versa. Is it the environment that’s changing the obesity rate, and is that affecting puberty? Or is accelerated puberty actually enhancing obesity? It’s really very interesting, and it’s going to be difficult to disentangle those different components. I do think there probably is a relationship, but I’m not sure it’s the entire story.

**Anna Rascouët-Paz:** Yes.

**Suzanne Fenton:** Tall girls may also have early breast development; they may be tall and thin girls. There’s something going on with growth and pubertal timing that we don’t have a good handle on yet, and that may really be at the crux of this entire problem.

**Anna Rascouët-Paz:** You work on rodents. What are some of the parallels and some of the differences? What are the questions that the rodents can’t really answer when it comes to humans?

**Suzanne Fenton:** That’s a really good question, too. We can study pubertal timing in rodents fairly easily because they have something called vaginal opening, at least in females. It’s a general indicator of puberty in females. Humans don’t have vaginal opening; that doesn’t exist, so some of the end points in puberty in girls and rodents are not the same, such as that one.

However, mammary gland development in a rodent is very similar to breast development in a girl. The stages of development are very similar; the hormones that control it, and the growth factors that are most critical in the cells that are involved, are all the same. That’s one of the things that we should be able to use a rodent model for: to evaluate breast timing in girls. Unfortunately, the more ovary-driven parts of it, like the cyclicity and the normal ovarian function, are pretty different between rodent models and humans.

**Anna Rascouët-Paz:** You’ve talked a lot about environmental chemicals, and there is a whole list of them that we don’t really know about or understand. Is there anything parents can do to prevent this from happening to their daughters?

**Suzanne Fenton:** Probably. People who really want their kids to have a healthy lifestyle would be helpful—for instance, if we could get our children to drink water, to carry it around with them in a metal, unlined water bottle; if we could find good sources of milk and dairy products that don’t have contaminating hormones and chemicals; and if we could have a better source of meats that are from animals that have not been given either drugs to enhance their growth or hormones to make them grow faster. That would be a great start.

We also have to help our kids understand that variety and changing things up in their life are probably a good thing, and they should probably try to stay away from a lot of the health and
beauty aid products until they’re older. Some of these things in general could help.

Anna Rascouët-Paz: Right.

Suzanne Fenton: It’s hard to nail down any one thing that’s contributing to this, so it may be a variety of things that need to change.

Anna Rascouët-Paz: What about the role of genetics in all of this? This affects girls pretty directly. Are these traits that they could transmit to their own children later on?

Suzanne Fenton: That is a good question. We don’t really have the answer for that. Early on in this epidemic—I’m going call it an epidemic because we don’t have control of it yet—pediatricians still thought that there was a role of genetics in all of this, but I don’t think that’s the case anymore. In fact, in recent conversations with pediatricians, it appears that they’re saying less often that this is because of hereditary reasons, and that it may have more to do with the growth trajectories in children. But, I think, not all pediatricians agree.

A lot of this may come back to training pediatricians in environmental health sciences, and having knowledgeable pediatricians talk to parents about this to help guide them in changing things in their children’s lifestyle that may eliminate environmental exposures.

Anna Rascouët-Paz: There was a story not that long ago in the New York Times about early puberty in girls, and they discussed it very much like a new normal. Many pediatricians seem to take the stance that there’s not much you can do about it, and that’s just the way it is. Should we treat it as a new normal, or can we aim at reversing these effects?

Suzanne Fenton: It depends on what we’re willing to put up with. I read that article, actually, and I think it was very good, but I think also that parents may want to have a stronger stand on this and say that, maybe, it’s not okay for this to be happening. I don’t think we’ve tried very hard to reverse the effects, so if parents and if educators say, “No, I don’t think this is okay,” we need to do something about this.

We could come up with some guidelines for healthy living that may help, but until we pinpoint some of the biggest problems, I’m not sure we can actually reverse it.

Anna Rascouët-Paz: It sounds like that’s a discussion that’s needed at the government level. We need to inform and educate both pediatricians and parents. Have you heard of anything happening in that direction, or is this something that needs to get started and needs more attention?

Suzanne Fenton: Some medical schools have enhanced their environmental health sciences aspects of the training that their doctors receive, and there are more CE classes that are being offered in that area. However, I don’t think that’s the norm. I also know that there are more grants available now, as in a translational biology area where clinicians and biologists could work together on questions such as this.

There may be a cohort of children—and people could do research in animal models on a very particular question related to pubertal timing. So there are some movements to enhance training and opportunities for research in this area, but I don’t think there are enough yet. This is affecting so many children that this should be a priority area for research.
Anna Rascouët-Paz: It does seem to be affecting girls from different ethnicities in different ways as well.

Suzanne Fenton: It does seem to be affecting African American or black girls more so than girls of other ethnicities, so there are some real issues here that need to be addressed, and enhanced funding of longitudinal studies, where children are recruited early in life and are followed all the way through puberty, and where there’s good measurement of their exposures. I’m not talking about only chemicals that are sprayed in their homes or in their schools, but if we had food sampling and enhanced biomonitoring in children, that would really help.

We don’t really have a good handle on what kids are exposed to. The National Health Report that’s put out by the Centers for Disease Control attempts to give us a real cross-cutting exposure [unintelligible] other people in the United States, but it doesn’t address the levels in children very well. There’s a very small population of children who are evaluated, and if we knew more about what it was in children that we should be studying, that might help.

Anna Rascouët-Paz: Thank you very much for joining us today.

Suzanne Fenton: My pleasure.

Anna Rascouët-Paz: You’ve been listening to Annual Reviews Audio. For 80 years, Annual Reviews has guided scientists to the essential research literature in the biomedical, life, physical, and social sciences. Learn more at annualreviews.org. I’m Anna Rascouët-Paz. Thanks for listening.