Welcome to the Huberman Lab Podcast where we discuss science and science-based tools for everyday life. I'm Andrew Huberman and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine. This podcast is separate from my teaching and research roles at Stanford. It is, however, part of my desire and effort to bring zero cost to consumer information about science and science-related tools. For the next four or so episodes we're going to be talking all about hormone effects on the brain and body. So that's a huge number of different topics. We're going to talk about sex. We're going to talk about reproduction. We're going to talk about puberty a little bit more. We talked about that in the previous episode. We're going to talk about menopause. We're going to talk about birth control. We are going to talk about aggression, competition, winning, losing. Basically we're going to cover as much about hormones as we possibly can in this month. And in doing so we are going to go deep into tools and protocols. We are also going to talk about a lot of tools that relate to things that you might not want to do in order to optimize hormone health regardless of stage of life or your goals etc. So it's sure to be a month rich with discussion, rich with tools and you're going to learn a lot of neuroscience and endocrinology. There's actually a field of neuroendocrinology. It's actually where I started my graduate work. I did a master's in it, which is only to say that I love the topic. I have a lot of friends that work on this topic, many of whom I've consulted for these episodes and I'm really excited to share the information with you. Before we dive into today's episode, all about emotions and sex. I want to just have a few announcements that are designed to point you to some useful resources. Last episode talking about the science of emotions and relationships. I mentioned the mood meter app. The mood meter app was developed by people out at Yale University who study the biology and psychology of emotions. It's a really wonderful app. However, many of you quickly told me that the mood meter app isn't available in your area. You went to the link we posted and it just was saying not available in your area. The situation was actually a lot worse than that. The situation was that when we recorded the episode, the mood meter app was working. I know because I downloaded a fresh copy of it to my phone. And then in the ensuing weekend, they took the mood meter app down for some repairs. The mood meter app is now up. It is available. I want to be really clear. It's not an app I'm affiliated with. I'm just mentioning it to you. They don't know me. I know them, but they don't know me. So we don't have any kind of business relationship. They do charge 99 cents for the app. I think the free version has disappeared in the last year or so. So that's mood meter app will provide the link again and the link should be working. Hopefully they won't take it down again in between this announcement and the release of this episode. I also just want to take a step back for a moment and talk a little bit about the logic of how to make the most of the information on the Heberman Lab podcast. I tend to throw a lot of information about a given topic. Many of you have pointed out, however, that I don't cover certain things. And once again, I'll just say the goal is always to be accurate, but there's no way I can be exhaustive. There's no way I can cover everything for a particular topic. The good news is we have time. My goal, at least in the first year of the Heberman Lab podcast is to give you a basis of foundation in these different topics of neural plasticity, focus, sleep, hormones, et cetera. And of course to provide tools along the way. We are going to host guests. I've actually started recording with some of these guests already. And even those episodes will include a little what we call primer, a little description of the basics of a given topic so that you can get more information from those topics. My goal really is to educate you in these topics, give you a foundation in these topics and allow you to start exploring them here in the episodes with our future guests, but also in other podcasts and books and other sources of information. So for those of you that are saying it's too much information, I just encourage you to remind yourself that you have a pause button. You can return to it. Everything's timestamp. For those of you that feel it's not enough information, I'm not covering enough. Just know that this is just the beginning. We intend to do this for a very long time. And we will be thorough over time. So thanks for your patience. And please be patient with yourselves. There's no reason why you have to digest all the information in one swoop. The other thing is that I've been told both that I speak too fast and speak too slow. So there's a wonderful solution to this. If I speak too fast or too slow, you can adjust the speed in YouTube. If you're listening in a different format, I think you also can adjust the speed of playback. So that's something that wouldn't be possible in the classroom, but you may find useful. And then last but not least, I want to point people again to this NSDR non-sleep deep rest protocol that the folks over at Made4 have put out as a free resource. It does, as many of you pointed out, bear resemblance to things like Yogan-Nidra, other forms of meditation. But what we've done is we've stripped out intentions or any kind of the the verbiage related to what some people might perceive as kind of related to the Yogan community or specific to kind of new AG type techniques. Not because we don't like Yogan-Nidra. In fact, I've done Yogan-Nidra daily for almost the last goodness eight years of my life. I love Yogan-Nidra. But sometimes the complicated language can be a separator and can discourage people from taking on these protocols that are extremely useful. So NSDR is intentionally generic. It's designed to bring you into a state of deep relaxation through a combination of breathing and body scan. There's the YouTube script over at Made4, which is linked in the caption. And many people find that they prefer that to scripts like Yogan-Nidra scripts where they're doing intentions and they're hearing a lot of kind of unusual language around the process. This is just very basic and I hope you'll enjoy it. And if you prefer the more typical Yogan-Nidra scripts, then go with those. There are many of them available on the internet and elsewhere. And last but not least, I want to point out that all our episodes now are subtitled both in English and in Spanish. So for those of you that prefer to digest this information in Spanish, that's now available to you in the subtitles. Today we're going to talk about the science of sex in particular sexual differentiation. Now that's a complicated topic because sex is both a adjective, a noun, and a verb depending on the context. Today we're going to talk about the hormonal effects and the neural effects of particular events that happen during development and how those guide adolescent and adult behavior, including sexual preference. It's an area that's fascinating and for which there are actually very solid textbook findings. So textbook findings means that there are many studies that have been aggregated over decades that point to what we now know to be used in. Now know to be absolute truths in terms of how hormones affect brain development, how the brain impacts hormonal development, and how those interact to control behavior, for instance. We are also going to talk about reproduction, the verb sex, and of course sex, the verb can also be carried out independent of reproduction. It's not always in particular in humans just to produce offspring. So that's going to be covered in the next episode, but you absolutely need to understand the information in this episode in order to make sense of the information in the next episode. So today we're going to explore hormones, what they are, how they work, what leads to masculinization or feminization of the brain and body. I'll just throw out one really interesting fact that perhaps most of you didn't realize that hormones have direct effects on the body. Most people know that because there are hormone differences and sex differences in bodies in terms of genitalia and body hair, distribution of body hair, etc. But there are also effects of hormones on the brain directly and believe it or not, there are also effects on the spinal cord on the neurons and structures within the spinal cord that impact in a very direct way what sorts of behaviors are possible. So it's a fascinating area. You might notice I'm going to go a little bit more slowly through this topic than I normally do. I want to be extremely careful with my language. Some of these topics, some of you may be thinking are extremely sensitive, right? And of course any discussion about sex and reproduction is a sensitive one, but today we're just talking about the biology. We're not getting into the cultural constraints or the cultural dialogue. What we're trying to do today is really get to the biology, the physiology, the endocrinology and the behavior. So let's start by talking about what hormones are just to remind you and what they do. Hormones by definition are a substance, a chemical that's released in one area of the body, typically from something we call a gland, although they can also be released from neurons, but they're released often from glands that travel and have effects both on that gland, but also on other organs and tissues in the body. And that differentiates hormones from things like neurotransmitters which tend to act more locally. So that's important. A hormone is a substance that's a creed at one location in the body, travels and has impact on things elsewhere in the body. Examples of tissues that produce hormones would be the thyroid, the testes, the ovaries, etc. And then of course there are areas of the brain like the hypothalamus and the pituitary which are closely related to one another and release hormones that cause the release of yet other hormones out in the body. So we're going to cover all this. If you don't know anything about endocrinology, you're still going to be able to understand today's discussion. And we're going to start with a discussion about what hormones actually do to create this thing that we call masculinization or feminization. So let's start with development. Spur meets egg. Everything that happens before that is a topic of the next episode. But sperm meets egg. This is mammalian reproduction. And that egg starts to duplicate. It starts to make more of itself. It makes more cells. And eventually some of those cells become skin, some of those cells become brain, some of those cells become muscle, some of those cells become fingers. All the stuff that makes up the brain and body plan. In addition, there are hormones that come both from the mother and from the developing baby, the developing fetus, that impact whether or not the brain will be what they call organized masculine or organized feminine. And as I say this, I want you to try and discard with the cultural connotations or your psychological connotations of what masculinization and feminization are because we're only centering on the biology. So typically people have either two excromasomes. And the traditional language around that is that person is female, right? Or an excromasome and a Y chromosome and that person will become male. Now it's not always the case. There are cases where it's X, X, Y where there are two excromasomes plus a Y chromosome. There are also cases where it's X, Y, Y where there are two Y chromosomes. And these have important biological and psychological impacts. So the first thing we need to establish is that there is something called chromosomal sex. Whether or not there are two X chromosomes or an X and Y chromosome is what we call chromosomal sex. But the next stage of separating out the sexes is what we call gonadal sex. Typically, not always, but typically if somebody has testes for their gonads, we think of them as male. And if somebody has ovaries, we think of them as female. Although that's not always the case either. But let's just explore the transition from chromosomal sex to gonadal sex because it's a fascinating one that we all went through in some form or another. So this X, Y that we typically think of as promoting masculinization of the fetus. We say that because on the Y chromosome, there are genes and those genes have particular functions that suppress female reproductive organs. So on the Y chromosome, there's a gene which encodes for something called malarion inhibiting hormone. So there's actually a hormone that's programmed by the Y chromosome that inhibits the formation of malarion ducts which are an important part of the female reproductive apparatus. That's critical because already we're seeing the transition between chromosome, Y chromosome, and gonad. And other genes on the Y chromosome promote the formation of testes. So there are genes like the SRI gene and other genes that promote the formation of testes while they also inhibit the formation of the malarion ducts. So the transition from chromosomal sex to gonadal sex is a very important distinction. It's kind of a fork in the road that happens very early in development while fetuses are still in the embryo. Now what's interesting as well is that just because there's a Y chromosome that can suppress malarion duct formation and there are other genes on the Y chromosome that promote testy development, the placenta itself is an endocrine organ. I think most people don't know this but the placenta is an endocrine organ as well. The mother, which of course is carrying the fetus, has an adrenal gland which can produce testosterone. There are instances for example where a mother has either a tumor or for some other reason is secreting large levels of testosterone while carrying a fetus that is XX. And that leads to what we would call masculinization of certain aspects of the fetus. Typically that would be in large clitoris. There are also some examples of other phenotypes on the body that are created even though it's a purely XX chromosomal baby. So we have to distinguish between chromosomal sex, gonadal sex, and then there's what we call hormonal sex which is the effects of the steroid hormones, estrogen and testosterone and their derivatives on what we call morphological sex or the shape of the baby and the human and the genitalia and the jaw and all these other things. And so it actually is quite complicated. So you know it's a long distance from chromosomes to gender identity and gender identity has a lot of social influences and roles. This is an area that right now is very dynamic and in the discussion out there as you know. But just getting from chromosomal sex to what we would call gonadal sex and hormonal sex and morphological sex involves a number of steps. So today we're going to talk about those steps and there's some fascinating things that do indeed relate to tools, do indeed relate to some important behavioral choices, important choices about things to avoid while pregnant. And for those of you that are not pregnant, things to avoid if you're thinking about eventually having children and that is not to drive development in one direction or another. But there are examples where there are some deleterious things in our environment that can actually negatively impact what we call sexual development overall regardless of chromosomal background. So let's get started with that. Let's talk a little bit more about what hormones do. Hormones generally have two categories of effects. They can either be very fast or they can be very slow. There are hormones like cortisol and adrenaline which act very fast. Dreneline can increase your heart rate. Very fast. It's secreted into the body. Cortisol can be a little bit slower but it also can have some very fast effects. And then there are hormones like testosterone and estrogen which we refer to as the sex steroid hormones. The sex steroid hormones can have quick effects through signaling meaning they can attach to cells and make those cells do different things. They can have actually quite quick effects on the brain. A lot of people don't know this but there are some very fast effects of estrogen and testosterone as well as long-term effects. These molecules for those of you that are interested are what it called lipophilic which just means that they like fatty stuff. They can actually pass through fatty membranes and because the outside of cells as well as what's called the nuclear envelope where all the DNA contents and stuff are stuffed inside are made of a lipid of fat. These steroid hormones can actually travel into cells and then get into the DNA, basically interact with the DNA of cells in order to control gene expression. So they can change the sorts of things that cells will become and they can change the way that cells function in a long-term way. That's actually how the presence of these genes like SRI and Moulinian inhibiting hormone lead to reductions or elimination I should say of things like the Moulinian ducts and promote instead what's called in males the Wolfian ducts or promote the development of testes rather than ovaries. All you need to know is that hormones have short-term and long-term effects and the long-term effects are actually related to their effects on genes and how those genes are expressed or repressed not to prevent them from having particular proteins made. So these hormones, these steroid hormones are exceedingly powerful and if we're going to have a discussion about masculinization or feminization etc. you also need to think about the counterpart it's not just about masculinizing the body or feminizing the body in brain it's also about demasculinizing the brain in many cases as a normal biological function of typically of XX females. And defeminization the suppression of certain pathways that are related to feminization of the body in brain but there are some really fascinating twists in this story. So I've just thrown a lot of biology at you but this is where it all starts to get incredibly surprising. You would think that it's straightforward right you have a Y chromosome you suppress the female reproductive pathway like the like the malaria index you promote this the development of testes and then testes make testosterone and then it organizes the brain male and it wants to do male like things and then in females you get estrogen and it wants to do a female like things and air quotes here for all of this and turns out that isn't how it works at all. Here's where it's interesting we have to understand that there are effects of these hormones testosterone and estrogen on what are called primary sexual characteristics which are the ones that you're born with secondary sexual characteristics which are the ones that show up in puberty and these are happening in the brain and body and spinal cord. So I'm going to disentangle all this for you by giving you some examples first let's talk about the development of primary sexual characteristics the ones that show up at birth and one of the more dramatic examples of this comes from the role of testosterone in creating the external genitalia. Now you might think it's just straightforward if there's a testes because there's a Y chromosome you got a gene that codes for the development of testes you get testosterone and the penis grows and the baby is born with the penis you know one of the first things that happens when the baby comes out as they look at the genitalia and they try and make an assessment whether or not it's a quote boy or it's a quote girl right there's been done for a very very long time in throughout human history. It turns out that it's not testosterone that's responsible for the development of the penis in a baby that has an X chromosome and a Y chromosome it's a different androgen androgen is just a category of hormones that includes testosterone but testosterone is converted in the fetus to something called dihydrotestosterone and that's accomplished through an enzyme called five alpha reductase. Now dihydrotestosterone has important effects later in life too. We will talk about those. In fact you just want to know dihydrotestosterone is what we would call the dominant androgen in males. It's responsible for aggression, it's responsible for a lot of muscular strength. It's involved in beard growth and male pattern baldness. We're going to talk about all of that but dihydrotestosterone has powerful effects in determining the genitalia while the baby is still in the embryo. There's testosterone that's made and that testosterone gets converted by this enzyme five alpha reductase in a little structure called the tubercle that tubercle will eventually become the penis. You say okay straight forward this testosterone is converted to dihydrotestosterone and then if there's dihydrotestosterone it controls penis growth and indeed that's the case. So that's a primary sexual characteristic. That baby will then grow up and later during puberty there will be the release of a molecule. I talked about this last episode called Kispeptin, K-I-S-P-E-P-T-I-N, Kispeptin which will cause the release of some other hormones, conatriode, releasing hormone, luteinizing hormone will stimulate the testes to make testosterone. So in puberty testosterone leads to further growth and development of the penis as well as the accumulation of or growth of pubicare, deepening in the voice, all the secondary sexual characteristics. So dihydrotestosterone creates what we would call the typical masculine phenotype for primary sexual characteristics and produces secondary sexual characteristics during puberty. There's a very interesting phenomenon that was published in the journal Science in the 1970s which now there's a wealth of scientific data and this relates to a genetic mutation where five alpha reductase, the enzyme that converts testosterone to dihydrotestosterone doesn't exist. It's mutated and weigh in a genome that it doesn't exist and this actually was first identified in the Dominican Republic, it has shown up elsewhere, it's quite rare but where it shows up it's robust. What happens is baby is born, typically when a baby is born they don't measure chromosomes, they don't look at chromosomal sex, XX or XY, that's not typically done nowadays. Baby is born, if you were to look at that baby it would look female, there would be very little or no external penis and so people would say it's a girl and they might have the celebration, it's a girl and I guess now they call them gender reveal parties or something like that, I don't know about this but anyway, they would reveal that the baby would reveal its external genitalia simply by being there and being naked when it's born, has nothing to do with gender. It has to do with genitalia and sex, that baby would be born and what was observed is that from time to time that baby after being raised as a girl, perfectly happy as a girl, would around the age of 11 or 12 or 13, would suddenly start to sprout a penis. The name for this is called Huevidosis which the translation is more or less penis at 12 and as strange as this might sound it makes sense if you understand the underlying mutation, what happens in these children, these Huevidosis is that the child is born, it has testes which are not descended so up in the body, they're not making a lot of testosterone early on. They weren't able to convert testosterone to dihydrogen testosterone because they lack this enzyme 5L for a ductase. As a consequence, the primary sexual characteristic of external male genitalia penis doesn't develop and then what happens is the baby grows up as a young child, essentially as treated as a girl, generally they report being pretty comfortable as girls although not always. Then testosterone starts getting secreted from the testes because the chest pepped in the brain signals through genitalia tropin and luteinizing hormone travels down to the testes, the testes start churning out testosterone and there's a secondary growth of the penis and all of a sudden there's a penis. This leads to some very complicated situations in families and culturally and actually the outcomes in terms of whether or not these children decide to self identify as males or females and how people treat them actually varies quite a lot. There's actually been a kind of adopting of a third category of sex and gender in these swevidosis for in order to just offer them the opportunity to explore not just what would be a typical kind of girl or woman or boy or man phenotype but something in between. Something that some people call intersex although intersex and pseudo hermaphrodidism is actually a separate thing altogether. So it's fascinating and the point here is that dihydrotestosterone, not testosterone is responsible for this primary growth of the penis and that testosterone later is involved in the secondary sexual characteristics, deepening in the voice, etc. Now this is where the information gets even more interesting and applies to essentially everybody. You might think that testosterone because it masculinizes the body in the secondary sexual characteristic way and because dihydrotestosterone, another antigen, masculinizes the primary sexual characteristics, the growth of the penis early on, that testosterone must masculinize the brain and there are in fact aspects of masculinization of the brain and body that are independent of genitalia. Now might be obvious to some of you but some people probably don't realize that. Yes indeed, the brain has receptors for testosterone. It also has receptors for estrogen but the fascinating thing is that if you look at the brains of people that have Y chromosomes and that have testes and that make testosterone and you look at the brains of people that don't have Y chromosomes or testes and therefore make far less testosterone in general. What you realize is that the cells in the brain that differ between what I'll call males and females but between XY and XX have receptors for testosterone but the masculinization of the brain is not accomplished by testosterone. I want to repeat this, the masculinization of the brain is not accomplished by testosterone. It is accomplished by estrogen. Testosterone can be converted into estrogen by an enzyme called aromatase. This is vitally important to understand. Testosterone can be converted into estrogen by something called aromatase. I'll give an example of where this happens later in life to just illustrate the principle and really embed it in your mind. During puberty in boys XY chromosome individuals it's not uncommon for there to be transient or sometimes long lasting breast bud development. Testosterone goes up during puberty for the reasons we talked about before and some of that testosterone gets converted into estrogen by an enzyme called aromatase. Aromatase is made by several sources in the body. One of the main sources is body fat so it can make a lot of aromatase. Sometimes you'll even see fairly dramatic breast development in males during puberty. Sometimes it's transient, sometimes it's not. The place where you see this is in athletes and bodybuilders that take a lot of anabolic steroids that take high levels of androgens so they'll be taking testosterone at super physiological doses. Sometimes not always, they will convert some of that testosterone into estrogen and they'll get what's called gynacomastia, which is the development of male breast tissue. Sometimes they'll get it cut out surgically. Other times they'll start trying to take estrogen blockers in order to try and suppress it or they'll try and block, block prolactin. It's a topic that we're going to get into in more detail. But what's important here is to understand that testosterone can be converted into the estrogen by aromatase. Aromatase is not just made in body fat. There are neurons in the brain that make aromatase and convert testosterone into estrogen and it is testosterone converted into estrogen. In other words, it's estrogen that masculinizes the xy individual that masculinizes the brain. This has profound effects on all sorts of things, on behavior, on outlook in the world, etc. But I think most people don't realize that it's estrogen that comes from testosterone that masculinizes the male brain, the xy brain, not testosterone nor dihydrotestosterone. So I just want to mention some tools. You might be asking yourself, how could tools possibly come up at this stage of the conversation where we're talking about sexual development and we're talking about the differentiation of tissues in the body? This is true both for children and parents and adults. I want to emphasize that there are things that are environmental and there are things that people use that in their homes sometimes that actually can impact hormone levels. And can impact sexual development in fairly profound ways. And I want to be very clear, this is not me pulling from some rare journal I've never heard of it. This is pulling from textbooks. In particular, today I'm guiding a lot of the conversation on work that on behavioral and her chronology. It was a book by Randy Nelson and Lance Creekfield, true experts in the field. I'm going to talk about some of the work from Tyrone Hayes from UC Berkeley about environmental toxins and their impacts on some of these things like testosterone and estrogen. I'm going to touch into them. They're going to give some anecdotal evidence that's grounded in studies, which we will provide in the caption or that all reference here. One of those that's actually really interesting but helps illustrate the principle that we've been talking about is a few years ago, there was a lot of excitement about evening primrose oil. Evening primrose oil is in a lot of products that typically are associated with skin beauty and skin health. And so I'm generalizing here, but typically it was mothers or sisters that were using it. And there were actually examples starting to crop up of young boys getting accelerated breastbud development from skin contact with women who were using evening primrose oil. So evening primrose oil is chemically a lot like estrogen and it has a lot of estrogenic compounds. There are a number of things out there like this. So believe it or not, things like pine pollen look very much like testosterone structurally. They are more or less are testosterone. Their bioavailability in humans isn't as clear. Evening primrose oil has a lot of estrogenic elements to it, just structurally how it's built. And so there were cases where boys were understandably being hugged by their mom or maybe even like showering and taking a using the evening primrose oil solution. Those things will actually change levels of estrogens in boys and girls. And so this wasn't just an issue for young boys. This was also an issue for young girls. So it's not that evening primrose oil is bad. It's just that many of you have probably heard about the dangers of soys and isoflavones and things like that. The impact of soy on estrogen levels is there are some decent evidence to support that. However, there's a lot of other factors that are more severe. And one of those is this evening primrose oil. So regardless of age, if let's just put it this way because people might be wanting to drive their hormones more estrogenic or more androgenic. And so how could I know what your preference is? I don't know. But in any case, things like evening primrose oil can actually promote estrogenic pathways in the body and some of it can go transdermal. Likewise, because testosterone replacement therapy is fairly widespread nowadays and some people accomplish that through cream, it's pretty well understood that if someone's taking that that they want to avoid contact with anyone skin contact with anyone that is trying to get it. And that is trying to promote more estrogenic activity in their body and especially in children. So that's one. The other is this issue of environmental factors. Now this, again, I'm just going to highlight, when one starts talking about environmental factors and how they're poisoning us or disrupting growth or fertility rates, it can start to sound a little bit crazy, except when you start to actually look at some of the real data. Data from quality research labs funded by federal government funded not from companies or other sources that are really aimed at understanding what the underlying biology is. And for that, I really, we, we should all be grateful to Tyrone Hayes at UC Berkeley. I remember way back when I was a graduate student in the late 90s goodness at UC Berkeley. And I remember him, he was studying frogs. He was talking about developmental defects in these frogs that live in different ways. It was California, but also elsewhere. And he identified a substance, which is present in a lot of waterways throughout this country and other countries. So US and beyond certainly not just restricted California, which is atrazine. This is ATRAZIN. Again, this is the stuff of textbooks. And it causes severe testicular malformations. So again, atrazine exposure is serious. And what's interesting is if you look at the data, what you find is that that sites in Western and Midwestern sections of the United States, 10 to 92% of male frogs, these were frogs mind you, had testicular abnormalities. And the most severe testicular malformations were in the testes rather than in the sperm. So it's actually the organ itself, the gonad itself. Now, it's very well known now that ATRAZIN is in many herbicides. And so, you know, whereas I would say in the 80s and 90s, the discussion around herbicides and their negative effects was considered kind of like hippy-dippy stuff or the stuff you hear about it. You know, the your local community markets and these kind of new AG communities. Now there's very solid data from federally funded labs at major universities that have impure reviewed and published excellent journals showing that indeed many of these herbicides can have negative effects primarily by impacting the ratios of these hormones in either the mothers or in the testes, altering the testes of the fathers or direct effects on developing young animals and potentially humans. And so you ask, well, what about humans? Frogs are wonderful, but what about what about humans? So here are the data on what's happening. And this isn't all going to be scary stuff. We're also going to talk about tools to emulinate and offset some of these effects. One would be be cautious with evening primrose as well as testosterone creams, depending on whether or not you want to be more androgenic or estrogenic, depending on your needs. But across human populations, sperm counts are indeed declining. Okay. So in 1940, the average, the average density of human sperm was 113 million per milliliter of semen. That's how it's measured. How many sperm per milliliter of semen? In 1990, this figure has dropped to 66, so one from 113 million per milliliter to 66 million per milliliter in the United States and Western Europe. So it's not just a US thing. Researchers also estimated that the volume of semen produced by men has dropped 20% in that time, reduced sperm count per ejaculation even further. So between 1981 and 1991, the ratio of normal spermatogenesis has decreased from 56.4% to 26.9%. So there's a lot that's happening primarily because of these herbicides that are in widespread use to reduce sperm counts. And these are going to have profound effects, not just on sperm counts, but on development, sexual development at the level of the gonads and the brain because you need testosterone to die hydro testosterone for primary sexual characteristics. You need estrogen that's come from testosterone to masculinate the brain. And of course, we're not just focusing on sperm and testosterone. You of course also know that many of these herbicides are disrupting estrogens in a similar way or are leading to hyperestrogenate estrogenic, excuse me, states which might explain why puberty is happening so much earlier in young girls these days. So there are a lot of things that are happening. Now does this mean that you have to run around and neuratically avoid anything that includes things like atrazine and should you be avoiding all kinds of herbicides? I don't know, that's up to you. But it does seem that these have pretty market effects in both the animal studies and in the human studies. You know, you can open up a textbook like the endocrinology textbook and think and find things like Vin Kloselin. This is V-I-N-C-L-O-Z-O-L-I-N, which is a fungicide. And it's an anti-androgen. You give it to animals to rats and instead of forming a penis, they don't form a penis. It's not that they form a clitoris, they just don't form a penis. So let's talk about female sexual development. And as always, what we'll do is we'll talk about the normal biology. Then we'll talk a little bit about an extraordinary or unusual set of cases. But we'll talk about them because they illustrate an important principle about how things work under typical circumstances. So there is a mutation called Androgen and Sensitivity Syndrome. And understanding how Androgen and Sensitivity Syndrome works can help you really understand how hormones impact sexual development. So here's how it works. There are individuals who are XY, so they have a Y chromosome, that are born that make testosterone, they have testes, and they don't have malaria index because they, because on the Y chromosome is this malaria and inhibiting hormone. However, these individuals look completely female. And in general, they report feeling like girls when they're young, women when they're older. But there's something unusual that's happening in these individuals because they have an XY chromosome type and not XX. So what's happening? Well, what's happening is the testes are making testosterone, but the receptor for testosterone is mutated. And therefore, the testes never descend. They don't have ovaries, they have testes, but the testes are internal. And so typically, these individuals find out that they are actually XY chromosomes, so that their chromosomal sex is male, if you will. And their gonadal sex is male. But the gonads, the testes are inside the body, they don't actually develop a scrotum, they don't make ovaries. And when they don't menstruate around the time of puberty, that's a sign that something is different. And so they never menstruate around puberty. And if they look into this deeply enough, what you find is that they are actually XY, they make testes, but their body can't make use of the testes, and that is because they don't have the receptors. And the receptors are vitally important for most all of the secondary sexual characteristics that we talked about, body hair, penis growth, that during puberty, et cetera. They live fairly happy lives, as females, although, of course, they can't conceive, right? They don't have a uterus, they don't have ovaries. So in general, don't produce sperm in quantities enough that they could actually reproduce with somebody, also, though sometimes they can. And believe it or not, and I'm not going to name names, but there are actually reports of several people, fairly prominent people throughout history, who have had this Androgen and Sensitivity Syndrome, or people suspected they did. And the reason to not name names is that it gets right to the heart of whether or not they are male or female. How could you say, right? They have XY chromosomes, but gonadily they have testes that are inside. And yet if you looked at their bodies, if you looked at their faces, you would say almost with certainty that they appeared female. And that naturally occurring experiment points to the fact that testosterone that shows up in the body and impacts the things at the levels of the receptor has a profound effect on phenotype, on the external or body plan. So again, we're talking about this in order to illustrate the principle that in order to have its effects, a hormone doesn't just have to be present, that hormone actually has to be able to bind its receptor and take action on the target cells. And once again, I'll just throw out the example of where people are using performance enhancing drugs, although that's a pretty broad statement. Nowadays there's a lot of excitement about the so-called SARMS, which are on the receptor side. And so we'll talk about this in a future episode. And I just say there's a teaser because the SARMS and what's happening right now in augmenting sports performance, both with testosterone directly, but also testosterone derivatives. And then also altering things at the level of the receptor is exceedingly interesting. And it's revealing to us the many ways in which hormones can impact brain and body. In ways that we didn't suspect. Perhaps the simplest way to understand how estrogen and testosterone impact masculinization or feminization of the brain and behavior is from a statement. It's actually the closing sentence of an abstract that my colleague, Naroa Sha at Stanford School of Medicine, published, which is that estrogen, again, it's estrogen that is a romanticized from testosterone by a Romancez, sets up the masculine repertoire of sexual and in animals and in humans, territorial behaviors. So it sets up the circuitry in the brain. Estrogen does that. Estrogen sets up the masculine circuitry in the brain. And testosterone is then what controls the display of those behaviors later in life. And I find that incredibly interesting, you would think it was just testosterone did one thing and estrogen did another, but it turns out that nature is far more interesting than that. Okay, so what are some things that impact sexual development early in life and later in life? Let's talk about cannabis. Let's talk about alcohol. And dare I say, let's talk about cell phones. Something that I never thought I would ever do either in this podcast or in the classroom, but these days, they're really interesting data and I think you should be aware of them. First of all, cannabis, marijuana, THC. I realize that there are now a lot of different variants on this. There are a lot of different strains of cannabis. I personally am not a pot smoker. It's just not for me. I'm not talking about the moral or legal implications, you know, in some states, it's decriminalized in other places. It's really legal in other places. It's basically legal. You have to check, you know, where you live and understand the laws. That's not what this is about. What we do know, however, is that with the exception of one study, there are many studies that point to the fact that THC and other things in cannabis promote significant increases in aromatece activity. Pot smoker's aren't going to like this, especially male pot smoker's aren't going to like this, but it's the reality. Remember, what you're hearing in the background is Costello snoring really loud. Should we put him on screen? He's not a cannabis smoker, but you can imagine why here. Come here. Come here. Come here. Come here. There you go. This dog definitely does not need cannabis. This is his state for most of the time. He's highly pregnant. He's asleep still. So some of you have asked to see Costello if you're just listening on audio, maybe he'll give us a note. That's a, oh, okay, we're going to let him get back to sleep. He's always here. Some of you have asked to see him. Costello is not a pot smoker either. He did have a dog sitter that was a pot smoker years ago. It was his favorite dog sitter, but I'm not a pot smoker. Again, no judgment, but here's the deal. That cannabis, and it's not clear if it's THC itself or other elements in the marijuana plant, promote aromatics activity. Now this has been observed anecdotally where pot smokers have a higher incidence of developing something I mentioned before, got a comastia, breast bud development, or full-blown breast development in males. There may be some women who want to increase their estrogenic activity. Remember, females make testosterone. It comes from the adrenals. They don't have testes, so it comes from the adrenals. That testosterone can also be aromatized, although typically most of the aromatase activity that we're referring to in these examples is in males. Testosterone can increase estrogenic activity, so you might say, oh, therefore does testosterone reduce sexual behavior, does it create all sorts of things that are related to low testosterone, not necessarily, not necessarily. Here's why. Estrogen itself in males and females is important for things like libido and sexual behavior. I'm going to repeat that. If estrogen is too low in males, it can actually inhibit libido and sexual behavior. You don't want estrogen too high or too low, whether or not your male or female. Of course in females, estrogen levels tend to be higher than in males. I'm speaking very generally here. You just think back to the chromosomal sex. That's what I'm referring to when I say male or female, although there's nuance there, of course. In females, the testosterone that comes from the adrenals has a powerful effect on libido and desire to reproduce. In the next episode, we're going to talk about how that works in its relationship to birth control, its relationship to menopause. We're also going to talk about how that whole thing works in males as well. But cannabis and other aspects of the marijuana plant can impact levels of testosterone and estrogen by increasing aromatase. We should be aware of that. As well, there are good data. I was able to find several studies on PubMed pointing to the fact that smoking marijuana during pregnancy can shift the pattern of hormones in the developing fetus such that it promotes more estrogenic outcomes. Now earlier I said that estrogen is what masculinizes the male brain. In utero, that's true. But the way that cannabis seems to work, at least from the studies I was able to identify, is that it promotes circulating estrogen in the body and therefore can counteract some of the masculinizing effects of things like testosterone and dihydrotestosterone on primary and secondary sexual characteristics. I mentioned this because I think nowadays marijuana use is far more widespread. Certainly during puberty, it can have profound effects on these hormonal systems. We'll do another episode that goes really deep into this, but yes, cannabis promotes estrogenic activity by increasing aromatase. Most everyone can appreciate that drinking during pregnancy is not good for the developing fetus. Fetal alcohol syndrome is a well-established negative outcome of pregnancy and it's something that they're cognitive effects that are really bad. There's actually physical malformation, etc. So drinking during pregnancy, not good, probably drinking during puberty, not good either because alcohol, in particular, certain things like beer but other grain alcohols, can increase estrogenic activity. Now, this isn't just about protecting young boys from estrogenic activity. It's also protecting girls from excessive or even hypoestrogenic effects of alcohol in puberty. Now many teenagers drink, college students drink, and it's important to point out that puberty doesn't start on one day and end on another day. puberty has a beginning, a middle and an end, but development is really our entire lifespan. This idea that puberty has us open and close, that's just false. We talked about cannabis, we talked about alcohol, let's talk about cell phones. First of all, I use a cell phone, I use it very often, and I do not think they are evil devices. I think that they require some discipline in order to make sure that it does not become a negative force in one's life. So I personally restrict the number of hours that I'm on the phone and in particular on social media. I only answer email at particular times of day. But what about the cell phone itself? When I was a junior professor, a pre-tenure early professor, I taught this class on neural circuits and health and disease. One of the students asked me, are cell phones safe for the brain? All the data pointed to the fact that they were, or at least there were no data showing that it wasn't. I still don't have the answer on that, frankly. I don't see a lot of studies about it. I'm not personally aware of any evidence in quality peer-reviewed studies showing that cell phones are bad for the brain or that holding the phone to the ear is bad or that Bluetooth is bad or any of that. I'm just not aware of any quality studies. If you are aware of quality studies, peer-reviewed studies, please reference them, put them in the comment section, send them to me however you like. I'd love to see them. I'm not aware of them. I was very interested in a particular study that was published back in 2013 on rats. It was basically took a cell phone and put it under a cage of rats and looked at basically testicular novarian development in rats and saw minor but still statistically significant defects in ovarian and testicular development. Since then, and now returning to the literature, I've seen an absolute explosion of studies, some of which are in quality journals, some of which are in what I would call not blue ribbon journals, identifying defects in testicular and or ovarian development by mere exposure to cell phone emitted waves. Let's just call that. We don't know what they are. And this sounds almost crazy, right? Anytime somebody starts talking about EMFs and things like that, you kind of worry like is this person okay? But look, the literature are pointing in a direction where chronic exposure of the gonads to cell phones could be creating serious issues in terms of the health at the cellular level and in terms of the output. So the output in for the testes would be sperm production, swimming speed and sperm. It is an important feature of sperm health. In the ovaries, it would be estrogenic output, how regular the cycles are. So in animals, the cycles are a little bit different than in humans. They don't have a menstrual cycle. They have an estrus cycle, which is generally around four days. I think that it's fair to say based on the literature that there are effects of cell phone emitted waves on gonadal development. The question is, what is the proximity of the cell phone to the gonads? Now I've taken the literature as I observe it and of course we'll point you to in the captions. I don't like to have my cell phone on and in my pocket. I'm well past puberty, but nonetheless some of these effects were seen in adult animals. There are effects now that have been demonstrated in humans, so let's just talk about a couple of those effects. So paper published in the journal Clinical Biochemistry from Escander et al. It's at hormone profiles and people based on proximity to their phone and frequency of phone use, where they stored their phone on their body, as well as proximity of where they lived to, I guess they're called these radio frequency towers, so the base stations. They were looking at effects of radio frequency radiation, RFR, on human hormone profiles. They show significant decreases in cortisol, you might say, well that might be good, but you need that morning cortisol bump in order to wake up, morning cortisol is good. But also thyroid hormones were significantly reduced, prolactin in young females, that's definitely concerning and testosterone levels in males and females. And so there are now quite good data showing that being close to the phone too much of the day and how close it is an interesting question. Living near one of these base stations, apparently can have effects on hormone profiles. And when you see a study like this one should always ask, well what are the other things that could also have effects on these hormone profiles, right? Because you could imagine that if you ran the same study of people that live close to a waterway or close to a highway where there's a lot of exhaust from buses and cars, you might see similar effects. So you have to take these sorts of studies with a grain of salt. I think it's very interesting and given that the last time I looked into these data were way back when I was a junior professor and there was like one or two studies that I could find, one of the studies pointed to increases in testosterone in rats where they had close proximity to these radio frequency radiation waves. And then in the other case it showed decreases in testosterone. So there really wasn't any conclusion. Take away from that now there's pretty impressive amount of data pointing to the fact that there are effects of these things on hormones. I don't know what to do with that information. I'm not going to stop using my phone but in light of the work from Tyrone Hayes and others looking at sperm counts and looking at the decrease in testosterone levels in sperm counts and fertility over the last 20, 30 years. Perhaps it's not surprising. Although there are again cell phones and smartphones have really been in prominent use mostly within the last 10 or 11 years and so it's hard to explain all of those declines simply on the basis of cell phone use. There's some interesting effects of hormones that actually you can observe on the outside of people that tell you something about not just their level of hormones but also about their underlying genetics. And these relate to beard growth and baldness and it's fascinating. The molecule, the hormone dihydrotestosterone made from testosterone, is the hormone primarily responsible for facial hair for beard growth as well. It's the molecule, the hormone primarily responsible for lack of hair on the head for hair loss. So how does that work? Well DHT circulates in the body and it binds to DHT receptors in the face to promote hair growth but it binds to DHT receptors on the scalp to promote hair loss. Not incidentally, the drugs that are designed to prevent hair loss are five alpha reductase inhibitors. So remember five alpha reductase from the hovedosis? Well, the people that discovered the hovedosis went on to do a lot of research on the underlying biochemistry of this really interesting molecule dihydrotestosterone. They identified five alpha reductase and five alpha reductase inhibitors are the basis of most of the anti hair loss treatments that are out there. And so there are some interesting things here. First of all, the side effect profiles of those treatments for hair loss are quite severe in many individuals. Remember DHT is the primary androgen for libido, for strength and connective tissue repair for aggression, even if that aggression of course is held in check, but just sort of ambition and aggression is related dopamine but within the testosterone pathway less so pure testosterone although pure testosterone has its effects. But DHT is at least in primate species including humans is the dominant androgen for most of those sorts of effects. And if you look at somebody, everyone can predict whether or not they're going to go balled based on looking at there. We're always taught our mother's father. So if your mother's father was bald, there's a higher probability that you're going to go bald. The pattern of DHT receptors on the scalp will dictate whether or not you're going to go bald everywhere or just in the front or crown type baldness. And the density of the beard tells you about the density of DHT receptors. Now this varies by background, by genetic background. And actually around the world nowadays because people travel and people form couples and have kids with so many different people of different mixed cultures, you're seeing this starting to disappear. But there are areas of the world where all the men seem to have the same pattern of baldness like a strip of baldness down the center with hair still on the sides and full beard. That's because these patterns of DHT receptors are genetically determined. That's where testosterone levels can still be very high. DHT levels in the blood can be very high and yet people will have very light beards or no beards. And that's because they don't have a lot of DHT receptors in the face. And still other cultures you'll see people with huge beards, tons of beards are growing all the way up to their eyes and they have huge heads of hair and that's because they have a lot of DHT receptors on the face and not on the scalp. So there are a lot of effects of DHT that you can just see in male phenotypes. And it's interesting that these hair loss drugs that are or to prevent hair loss drugs are directly aimed at preventing the conversion of testosterone into dihydrotestosterone. And that's why they to some extent prevent hair loss but also to some extent have a bunch of side effects that are associated with low DHT. On these lines there's a particular sports supplement that a lot of people use called creatine. Creatine now there's a lot of research showing that creatine can bring more water into the muscle. It can support strength. It does a number of other things. Might even have some important cognitive promote, cognitive enhancement effects, although mild. The studies there show that it can be significant. Some people, not all, it's more anecdotal, report that creatine promotes hair loss. It differs by individual. For some people that's true, for others, no. But yes, it does appear based on the studies I was able to find on PubMed that creatine does promote five alpha reductase activity. And therefore the conversion of testosterone into dihydrotestosterone. And so it makes sense that it might promote some degree of hair loss as well as beard growth as well as the other effects of DHT. I recall in junior high school and middle school going home one summer, seventh grade coming back in the eighth grade. And a kid that I knew that I was friends with went from being like a young kid to, it was like a grown man. He had a full beard. It was amazing. It was like it would completely transform. I mean, puberty as I've said before is without a doubt the most accelerated rate of development that we will go through at any point in our lives, even faster than infancy. In terms of the huge number of different cognitive changes and physical changes. Not surprisingly that same individual was mostly or bald by his early 20s. And that's because he must have had just exceedingly high levels of DHT. I also played soccer with this kid and he was basically like dribbling past everybody. It was like a grown man playing soccer with a bunch of little kids. Full beard, you know, bald at 20. And so the rate of maturation, the rate of aging is very interesting. It's hard to know rate of aging. There's some genetic tests that now can allow you to do that. Things like Horevath clocks and things of that sort. A beautiful work of David Sinclair at Harvard and others has pointed to this. The speed of entry and exit from puberty might be, putting out there as a hypothesis, might be an interesting window into how fast one is going through their aging or developmental arc because development, of course, doesn't just start at birth and then after puberty it continues your entire life. So I think it's interesting. You will often see that people, boys and girls, I should say boys or girls, will develop secondary sexual characteristics at different rates. And sometimes it's sequential. You know, you might see a kid will show grow very tall or show have a big growth spurt. But then breast development will come a little bit later and then other features will come a little bit later. You can also see this in boys, the person that I referred to earlier, my friend that developed full beard, you know, went bald. He was also quite muscular. He's a great athlete. So he went through puberty exceedingly fast. Other people go through it more slowly. Some people will go through puberty at age 14, but they won't start to accumulate facial hair until much, much later. Or their voice will change first very early and then they won't get the other secondary sexual characteristics until much later. And so we don't really know how that impacts or relates to overall trajectory or rate of aging, but it's an interesting thing to think about for each and every one of us. I'm going to offer you the opportunity to do an experiment today while listening to the podcast. But first I want to tell you a story about hyenas, professional baseball and clitoris is the size of penises. So when I was a graduate student at UC Berkeley, we had a professor in our department, phenomenal scientist, a Steve Glickman. Steve Glickman had a colony of hyenas, spotted hyenas that lived with engaged enclosures, of course, in Tilden Park behind the UC Berkeley campus. The enclosures are actually still there. I run past there fairly often. The hyenas are no longer there. This was a federally funded field station. These animals were brought over from Africa or were bred there. And the reason why they were hyenas in Tilden Park enclosed in Tilden Park was because hyenas exhibit an incredible feature to their body, their hormones and their social structure. Because unlike many species, have a situation with their genitalia where the male penis is actually smaller than the female clitoris. And I should say that the male penis itself, having seen a fair number of hyena penises, is not particularly small, which means that the hyena clitorises are extremely large. This was well known for some time. It turns out that in these spotted hyenas, the females are dominant. So after a kill, the females will eat, then their young will eat, and then the male hyenas will eat. As well, when the female hyena gives birth, she gives birth not through the vaginal canal that we're accustomed to seeing, but through a very enlarged clitoris like phallus, although it's not a phallus, it's a clitoris. And it literally splits open. So many fetuses die during the course of hyena development and birth. These animals have this, what could only be described as a very large or giant clitoris, although for a hyena, it's not giant, it's normal, and it splits open, and the baby actually comes through, the baby hyena actually comes through the tissue, and it's a very traumatic birth. A lot of tissue is torn away, et cetera. And as I mentioned, a lot of baby hyenas die. It was a mystery as to how the female hyenas have this, we'll call it masculinization, but it's really a Androgenization of the periphery of the genitalia. And it turns out, through a lot of careful research done by Steve Glichman, Christine Dre, and others, that it's interesting dion. What is essentially a pro-hormone to testosterone? It's interesting dion at very high levels that's produced in female hyenas that creates this enlargement of their genitalia. So if you want to read up on interesting dion, interesting dion is made into testosterone through this enzyme, 17 beta hydroxysteroid dehydrogenase. It's a complicated pathway to pronounce. It's a fairly straightforward pathway biochemically. You may recall, during the 90s and 2000s, there were a lot of performance enhancing drug scandals in particular in Major League Baseball. And it was purported, although I don't know that it was ever verified, but it was purported, that the major performance enhancing drug of abuse at that time, in particular players, whose names we won't mention, but you can Google it if you want to find out, was the Anderstine dion. It was sold over the counter. A lot has changed since then. But it's interesting that these hyenas with these highly-androgenized genitalia accomplish that through high levels of Anderstine dion in the females. Now if that's unusual, what might be even more unusual is that a graduate student that I was working with at the time. Alongside, we didn't share research. Her name was Nikola Sipka. She is actually a trained behavioral animal behavioral expert. She had trained ferrets for that show, the Beast Master, and she trained wolves for television shows and was a dog trainer. She had these two large dogs that, unlike my dog, would actually listen to her when she would give them commands. A remarkable scientist. She was studying a species of mole that also lived in Tilden Park. People are going to start to wonder about Tilden Park. What's in Tilden Park? But this particular mole that lived there had testes for part of the year and had the capacity to trans-differentiate its testes into ovaries in order to balance out the ratio of males and females in the population to keep reproduction at appropriate levels for that certain population. So some animals are actually able to adjust whether or not they have androgenized or estrogenized gonads in order to adjust the ratios of offspring or the males and females in there for promote offspring. The last little anecdote about this, which is also published in the scientific literature, which is weird, but I do find interesting. Formones are so fascinating, they're just incredible to me, is going back to the marijuana plant. The marijuana plant has these estrogenic properties. I asked a plant biologist whether or not this was unusual. I asked because there's all this stuff out there about, oh, soy does this and these plants are highly estrogenic, etc. Although we should probably point out that a lot of factory meats are also estrogenic. This isn't a meat versus plant's thing, but this plant biologist told me, oh yeah, there are plants that make what is essentially the equivalent of testosterone, like pine pollen, this looks a lot like testosterone, and there are other plants that make what is essentially estrogen. I said, well, why would they do that? Well, they said, and plants, at least as far as I know, don't have a consciousness, they don't have a brain, they don't have neurons even. But his answer was fascinating. He said that one of the reasons why some plants have evolved this capacity to increase estrogen levels in animals that smoke, not smoke it, but then animals that consume them, I'm guessing that animals aren't smoking marijuana, although, I don't know, send me the paper if you've heard of this, is that plants have figured out ways, they've adapted ways to push back on populations of rodents and other species of animals that eat them. So plants are engaged in a kind of plant to animal warfare where they increase the estrogen of the males in that population to lower the sperm counts to keep those populations clamped at certain levels so that those plants can continue to flourish, even if those animals are reproducing very robustly. I find this just fascinating, and hormones, therefore, aren't just impacting tissue growth and development within the individual and between the mother, remember the placenta as an endocrine organ and the offspring, but plants and animals are in this communication. And today we're in this communication, I'm telling you that there are certain herbicides that humans are using for which there's very good data are disrupting the endocrine pathways. And so it's fascinating that humans and other animals were always in this interplay with plants and the other things in our environment. And hormones and adjusting the hormone levels of animals and plants is one way in which the environment kind of pushes back or pushes forward, if you will, in terms of promoting their well-being and longevity, as well as you trying to promote your well-being and longevity. If anyone wants to see the incredible paper by Steve Glickman and colleagues, it was published in the Procings of the National Academy first in 1987. That's Glickman at all. That was the hypothesis that it was Anderstin Dione. And then if you just Google Glickman Hyenas Science Magazine, there's a beautiful cover article and feature all about that important discovery. It's a fascinating one. And I should mention also that those discoveries, both the moles and the hyenas weren't just impactful for the world of animal behavior and endocrinology. They've also strongly impacted understanding of conditions that show up in the clinic, which we haven't talked about today, which is actually pseudohermaphroditism. Occasionally babies will be born where it is unclear if they are boys or girls based on the genitalia. And this has a very important ethical and other issues. Do you raise them as a boy or a girl? It's not super uncommon for this to happen. And there have been terrible cases where people have gone against the chromosomal sex. And the person was very unhappy with the choice that their parents had made for them. There were also cases where they've gone with the chromosomal sex and the person was very happy about the outcome. There have been cases where they've been treated with hormones and there have been cases where they have not been treated with hormones. It's a complicated literature. And it has to be sorted out on kind of a case-by-case basis. But it is something that does happen. And the studies on interesting dionin hyenas and in these very interesting moles, pseudohermaphroditic moles that live in Tilden Park have impacted not just the science but the therapeutics around those important issues. So now, last but not least, I want to discuss the effects of hormones while you and I were separately in utero and the effects that that had on who we are, who we select as mates. So mate choice, sexual preference, and all other aspects of what you would call sexual development. Now this is something that's gotten a lot of popular press and it has to do with how exposure to Androgens in particular while we were in utero impacted whether or not people report as homosexual, heterosexual, identify as male or female. I'm very familiar with this work because I was a graduate student in the department that first published this work and I'm an author on the paper. I was not the main driver of the work but I was involved in the work and I certainly know the people that did this work. First it starts with a story. There was a researcher who's still going now, his name is Dennis McFadden. I believe it was at UT Austin back then and he was studying the auditory system and people come into his clinic and he would or his laboratory and he would look at hearing and he would explore different aspects of what they call the psychophysics of hearing and understanding hearing thresholds and frequency thresholds and he made several observations and those observations were that young males tended to have what are called auto acoustic emissions more often than young females did. Auto acoustic emissions as the name suggests are the ears actually making sounds. Now these sounds have to be picked up by a special apparatus because they can hear into that frequency but turns out the ears don't just take sound waves and convert them into these things that we this thing we call hearing but they also in some cases make sounds so your ears are making sounds strange right. So it turns out that there's a sex difference in auto acoustic emissions. Turns out also that people that self report as lesbians they also have auto acoustic emissions significantly more than females that don't self report as lesbians and Dennis noticed this and published this and it was an important discovery because it was one of the first discoveries that they're that pointed to the fact that there are sex differences in biology that are independent of sex. I mean this is hearing and auto acoustic emissions and just to really illustrate what that what the former problem was and why this study was so important. A lot of people had explored for instance whether or not homosexuals had lower testosterone for instance in males and actually the result often was the opposite that gay men or men that self report is gay often had much higher testosterone and those studies then became controversial because people said well you know sexual behavior can relate to testosterone etc. It became very controversial and then there were some studies that attempted to look at the equivalent phenomenon in people that self report as lesbian or self report as heterosexual and so it became very complicated but this was an identification of a phenomenon auto acoustic emissions that was independent of anything that had to do with sexual or even social behavior. 1998 rolls around and I'm a graduate student at UC Berkeley and a guy by the name of Mark Breedlove kind of an ironic name given that he worked he worked and still works on sexual dimorphism in the brain and in the spinal cord and nervous system and Mark who's phenomenal scientist comes running down the hall I'll never forget this and he said give me your hands. He's like give me your hands and he pulls out a ruler and he starts measuring my fingers and he takes down a couple measurements and then he goes away and I'm like what was that? Well I was in a course that Mark was teaching at that point and soon after we did a study that Mark directed exploring the finger length ratios and I'll explain what those are of males and females and people that self reported as homosexual or heterosexual. So let's just get to the basic what we'll call sex differences first. These are averages I want to point out anytime you get into this kind of topic people are assume it's causal but it's not causal these are averages that I'm about to report. It is the case that the ratio of what's called the D2 to D4 digits so the D2 is your index finger so your thumb is D1 then D2 would be your index finger that you would point with middle finger is D3 which you whatever with and then D4 is this so called ring finger and D5 is the pinky. It is the case that the D2 to D4 ratio is greater in self reported females than it is in males. What does that mean? It means that the digit D2 and D4 are more similar in length in females than in males and the effect is particularly excuse me pronounced on the right hand although not always okay. And does not have to do with handedness. It's D2 to D4 difference has to be measured correctly. You can't just look at somebody's hands and say oh you know their ring finger and index finger are very similar and therefore they are female in you know where they were exposed to very little testosterone in utero. You can't look at somebody and see that their index finger is much shorter than their ring finger and say oh you know they must have been exposed to a lot of androgen. You have to actually measure it and you have to measure it correctly. You have to measure it from the base of the finger where there is that first crease all the way to the tip past the you can't include the fingernails if you are going fingernails you will be logical here folks. So you can't normally see it from the back of the hand although I don't know if this will show up here but if you look at the back of the hand sometimes you can see it you know my case for instance let me see if I can do this. So my D4 is a little bit longer than my D2. And some people it's more pronounced and that's on my right hand. On the other hand the difference actually is far less pronounced. It's a little bit it's a little bit pronounced there but not so much okay. So that's sort of the typical ratio that you would see. Turns out that in mice and in humans the more androgen that you were exposed to in utero the smaller the D4, D2 ratio meaning that the ring finger tends to be slightly longer than the pointer finger. And in females because they're exposed to less androgen in utero typically then those fingers tend to be more equal and late. And these are subtle differences and these are averages. I invite you to look up the paper. This was published in Nature in 2000 and it's been replicated six times. Now here's where it gets even more interesting and potentially precarious so we're going to step cautiously here. If you look at the finger length ratios of men that self-report as homosexual they have either the typical male pattern of D2 to D4 ratio or a hypermasculinized D4 to D2 ratio. Now this can't be something that's established or modified by behavior. This has to be something that was established in utero and in fact it's present at birth. So it completely divorces the interactions between hormones and behavior. And that's an important theme that we've been talking about and we're going to talk about even more next episode is that hormones impact behavior but behavior also impact hormones. But this is a case of hormones impacting what really should be considered a primary sexual characteristic because it doesn't show up in puberty. It shows up before puberty. It's actually established in utero. And in people that self-reported lesbians and I remember going out there and collecting these data with these collaborators on this work. Again, I wasn't the main driver on the work but I participated in some of the analysis. People that self-reported lesbians also tend to have a smaller D2 to D4 ratio. So this is consistent with the autochoustic emission study that Denis McFadden had published. And it points to the fact that early exposure to Androgens may have an impact not just on Androgensization of the body plan but also separately on sexual preference. Now this raises all sorts of interesting questions about biological basis of sexual preference. I'll tell you about another study. A guy named Simon LeVay who is at UCLA who trained under Hubel and Wiesel. If any of you remember early episodes on plasticity, David Hubel and Torrenson Wiesel, my scientific great-grandparents won the Nobel Prize for discovery of critical periods for brain plasticity. They define some of the most important aspects of how we see and brain plasticity. Simon LeVay trained with them and then Simon went on to discover that in the brains of people that self-report homosexual, there is a brain difference. And the brain difference is in an area called the interstitial nucleus of the anterior hypothalamus. So it's the INAH. And so there are published reports that was published in science. The other work I refer to was published in Nature and then replicated no fewer than six times and the McFadden results that point to strong biological correlates of mate choice of sexual preference. And these tied directly to things like androgenization or estrogenization, meaning we could call it maleness or femaleness, but that sort of tricky territory because of the way that we described the huge range in which sex can be defined earlier. So if you want to measure D2D4 ratio, you're welcome to, but you also have to understand that it's not predictive of anything, right? It's just a window into the possible androgen exposure that you had early in life. There are plenty of heterosexual men who report themselves as heterosexual who are out there, who have similar or have D2D4 ratios to females. And there are plenty of females whose index fingers are shorter than their ring fingers and they're perfectly happy or they say they're perfectly happy and we are inclined to believe them being heterosexual. So there's variation. In fact, Mark tells a really good joke. If you want to know whether or not somebody is homosexual or heterosexual, simply look at their hands, look at their D2D4 ratio and guess heterosexual and you'll be right 96% of the time because 96% of the time people report themselves as heterosexual on average. Those numbers might be changing. So the joke really is a joke on science because that falls within the realm of statistical significance and yet it really illustrates the fact that none of this is causal. But it's nonetheless very interesting because it means that hormones are organizing the brain early in development in ways that can potentially impact same or opposite sex partner choice later in life. Now of course there are other things that can impact opposite sex or same sex partner choice later in life. The study did not look at people who reported bisexual. There hasn't been a lot of studies on that yet. One thing that's very interesting for which there's some good scientific data but there's also some controversy is that it appears that the probability of a male human, self-reporting as homosexual, increases with the number of older brothers that he has. Now that doesn't mean if you have an older brother or even if you have 10 older brothers that you are sure to self-report as homosexual. But statistically it becomes more likely that somebody will with each successive older brother that they have. And the idea that starting to emerge in the developmental neuroendocrinology landscape is that there's a record within the mother of how many male fetuses she's carried because male fetuses are secreting certain things, dihydrotest, austroen, other things that can feed back onto the genome. So these could be epigenomic effects or onto the placenta itself so that there's a higher probability and subsequent pregnancies that offspring will self-report as homosexual. So it's a fascinating area of biology. And as you've noticed today, none of this deals with the current controversies around gender and how many genders and sex, etc. That's a separate conversation that is by definition grounded in the kind of concepts we've been talking about today and needs to take place, taking into consideration all of the aspects of sex and the effects of hormones both on the body, on the brain. We didn't talk a lot about spinal cord, but we will in the next episode on, but we can just say on the brain and the periphery, early effects, late effects, acute effects, meaning effects that are very fast of levels of hormones going up or down, something that absolutely happens during the, and across the menstrual cycle, as well as long-term effects like the effects of these hormones on gene expression. So today, as always, we weren't able to cover all things related to sex and hormones and sexual differentiation or development. There's no way we could, but we have covered a lot of material. We talked about some effects of environmental toxins. We talked about potential effects of cell phone radiation, something I never thought that I would be talking about, especially not in a podcast, but for which there are interesting emerging data. We talked about considerations about evening primrose oil and its estrogenic effects, about creatine and its pro-DHT effects, about cannabis, alcohol, about plants exerting warfare on animals by increasing aromatase, the conversion of testosterone to estrogen. We talked about hyenas with giant clitoruses and we talked about moles that can convert from having ovaries to testicles. And throughout this, Costello has been snoring nonstop. He missed all of it, although he might be learning it in his sleep for all I know. And I do understand it's a lot of information, a lot of detail. As always, I just want to remind you, you don't have to absorb all the information at once. Next episode, we are going to be talking about the science of sex, the verb, actual reproduction. We're also going to be talking about effects of hormones on various aspects of behavior and ways to modulate hormones through the use of behavior, supplementation. Also we'll touch on diet and nutrition a bit. We're going to talk about interactions between those things and behavior as they relate to important themes like sex and reproduction, like workplace performance, like motivation and drive and even anxiety. There's a very interesting relationship between hormones and anxiety and the desire to explore novelty. So just remember as we go forward that hormones affect behavior and behavior affects hormones, but that doesn't mean that cutting off your index finger will increase your testosterone. Many of you have asked how you can help support the podcast and we thank you for the question. There are several ways to do that. The first one is to subscribe on YouTube. 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