2. Brain

To review Chapter 1, the female orgasm system is outlined in the following sketch.

Every part of the system should work at the same time. *If any one part of the system goes wrong, the whole system will not work.*

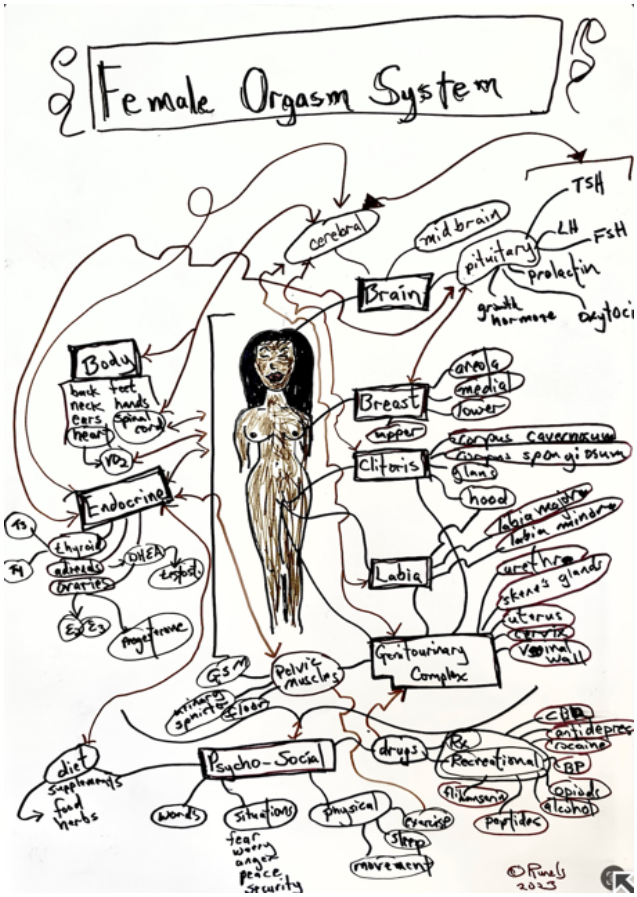

Figure 1. The Female Orgasm System as defined by the main parts to be considered by the clinician treating decreased libido and anorgasmia. The blocks and circles represent parts of the system. The lines represent the flow of information from one part to another.

Why Every Part Must Work, So You Must Know About Every Part

Consider the respiratory system.

If you took out the red blood cells, it wouldn't work. Take out the alveoli; it wouldn't work. Add a foreign body to the trachea so air cannot flow; it will not work.

This idea that *every necessary part needs to function, whether we are aware of every part or not*, is obvious in the respiratory system, and we think automatically in terms of systems analysis when thinking about treating dyspnea.

It seems to me that when we think about treatment for every disease process, we think in terms of systems—except for sexual dysfunction. We (you and I and the others studying this course) hope to change that.

To review, the purpose of this course is not to dive deeply into any one part of the orgasm system (which is different from the reproductive system); the purpose of this course is to make plain the elegance and the complexity of the female orgasm system (its major parts and their connections) so that none of the following three things happens:

(1) We *over*estimate the importance of any singular therapy.

(2) We *under*estimate the importance of any one part of the system and, therefore, ignore a possible therapy.

(3) We are unaware of an important part of the system and, therefore, never offer a potential therapy that addresses the dysfunction of that unrecognized part.

The idea that systems analysis is ignored mostly in sexual medicine became obvious to me because, after three decades in medicine, I don't know another branch of medicine where I am as likely to hear the following statement: “That ____ doesn't work,” where you can fill in the blank with anything used for treating sexual dysfunction.

The failed therapy could be flibanserin; it could be sex therapy; it could be our O-Shot® procedure; it could be any legitimate therapy used to treat sexual dysfunction. I often hear the previous statement made without mentioning the problem being treated and without discussion of other parts of the system.

Therefore, the statement, "It doesn't work," is often made without considering that perhaps "it" *does* work, but "it" was intended to treat a part of the system not broken in the patient being considered. Or "it" should have been used in combination with other therapies because more than one part of the system is broken.

I seldom see failure to use system analysis mistakes in other branches of medicine.

For the system to work,
Every part of the system must work,
Even the parts about which we are unaware,
Even the parts about which we choose not to care.

So, *we intend, with this course, to do a quick survey of the whole system* so that we can automatically use a systems analysis approach to sexual medicine discussions—considering all the first-order affecting parts; then, both our colleagues and our patients will more likely think in terms of systems in the area of sexual arousal, just like they do with other body functions.

The last chapter, Chapter 1, considered the main ideas that govern the formal *science of systems analysis*; now, we will use those ideas examine each of the main parts of the system, starting with the brain.

The Brain Is Central to the Female Orgasm System

Look at the following sketch of the brain; notice *the pituitary gland is part of the brain.*

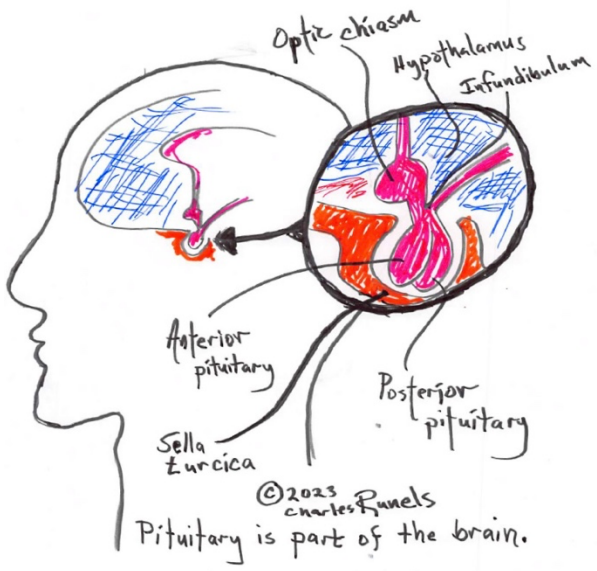

Figure 2. The pituitary is part of the brain. The brain governs the pituitary (along with feedback from blood hormone levels); the pituitary governs all the glands; the hormones from the glands govern the body.

One of the ways thoughts profoundly affect health is by the way thoughts affect the function of the pituitary gland. Whether it is severe grief, hope, or depression—all emotions affect what hormones the pituitary excretes, the pituitary hormones affect all the other glands of the body, and those glands secrete hormones that control the metabolism and function of the entire body—all of it.

To prove that thoughts affect the whole body by affecting the pituitary, consider what would happen if you suddenly smelled smoke and the fire alarm went off in the building where you now sit: you would likely instantly demonstrate tachycardia and a change in blood pressure. Those *physiological changes in body chemistry and function would occur because your thoughts told the hypothalamus to tell the*

pituitary to release hormones into the bloodstream that caused activation of the sympathetic nervous system, causing tachycardia and increased blood pressure.

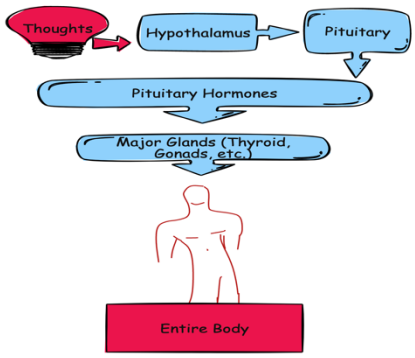

Figure 3. By changing pituitary gland secretion, thoughts can change the entire body.

So, your cerebral cortex (your thoughts) tells the hypothalamus to tell the pituitary to talk to the whole body. Thoughts affect the pituitary; *the pituitary hormones affect all the other glands and the body's metabolism and, of course, affect sexuality.*

When a woman talks with a sex therapist, she not only changes her behavior and sexual activities, and then those activities directly affect body stimulation and her interaction with her lover, but she also (by affecting her thoughts) changes her brain chemistry, the function of the pituitary gland, and so the metabolism and function of the entire body.

For further consideration that thoughts and brain chemistry affect libido, consider that *the only two currently FDA-approved drugs that are FDA approved to improve libido in women are both drugs that affect brain chemistry—not the genitalia.*

Sex History Repeating Itself

In the 1980s, urologists were taught to become sex therapists because it was thought that 80% of erectile dysfunction was psychogenic in origin. Then, after Viagra came to market, we discovered that 80% of erectile dysfunction (ED) was secondary to neurovascular changes in the penis; 80% of ED is caused by neurovascular, not by psychiatric causes. Now, with women, we can see the same mentality:

Our current FDA-approved drug menu for women includes two drugs:

1. Flibanserin (Addyi) decreases serotonin activity and increases dopamine and norepinephrine activity in the brain.

2. Bremelanotide (Vyleesi) activates melanocortin receptors.

Testosterone is also known to increase sexual desire in women, but there is no FDA-approved form of testosterone for women.

The only two FDA-approved drugs for improving sex in women are psychiatric drugs.

Options for Men Outnumber Those for Women

For comparison, in men, we have all the following drugs approved by the FDA for use with sexual dysfunction:

1. For erectile dysfunction:
    a. Viagra, one of the most well-known drugs for ED, it increases blood flow to the penis to help achieve an erection.

b. Tadalafil (Cialis): Another PDE5 inhibitor, it can be taken daily or as needed.
c. Vardenafil (Levitra, Staxyn): Available in both tablet and dissolvable form.
d. Avanafil (Stendra): A newer PDE5 inhibitor with a rapid onset of action.
e. Alprostadil: Available in an injectable form (Caverject, Edex) and as a urethral suppository (MUSE), it helps increase blood flow to the penis.

2. Premature ejaculation (PE) Treatment:
a. Dapoxetine (Priligy) While not approved by the FDA for use in the U.S., this SSRI is specifically for PE and is available in some countries.
b. Off-label use of other SSRIs and certain analgesic creams are also sometimes prescribed in the U.S. for PE.
c. Topical lidocaine (Promescent)

3. Testosterone replacement therapy:
a. For men diagnosed with hypogonadism (low testosterone levels), testosterone replacement therapy can be prescribed. It's available in various forms, including
b. gels,
c. patches,
d. injections,
e. and implants.

4. Penile implants

Notice that, on the list for FDA-approved therapies for men, the only therapies that work primarily by affecting brain chemistry are the SSRIs for premature ejaculation. All the other drugs and surgeries affect the genitalia.[1]

Do the available treatments for sexual dysfunction for men compared with those for women seem balanced to you?

We need more therapies that affect the rest of the female orgasm system—it is not all about the brain!

But the brain is a critical part of the system, and our current brain drugs for libido and orgasm in women have a place. So, let's think more about how the brain affects the system. We'll talk in more detail about sex hormones, like testosterone, in a later lesson.

A Simplified Version of the Female Orgasm System Parts

Here is a simplified version of the orgasm system.

Remember, if you look at formal systems analysis in a visual model, an important part of thinking includes both reinforcing and balancing feedback loops, both of which occur in sexual medicine.

Figure 4. A simplified version of the female orgasm system; subparts and feedback loops are removed. Some expansion of the brain component is included. CB-cerebral hemispheres; MB-midbrain; Pit-pituitary; FSH-follicle stimulating hormone; TSH-thyroid stimulating hormone; LH-leutenizing hormone; GH-growth hormone.

[1] Testosterone also affects brain chemistry. But there is a receptor on every tissue type for testosterone (bone, muscle, skin, heart, and of course the penis). So, unlike all of our current FDA-approved drugs to help women with libido, testosterone is much more than just a brain drug. But, we have not FDA-approved testosterone for women.

If you were thinking about the population, the size of the population would have a balancing effect in that the more people who are born, the more people who die.

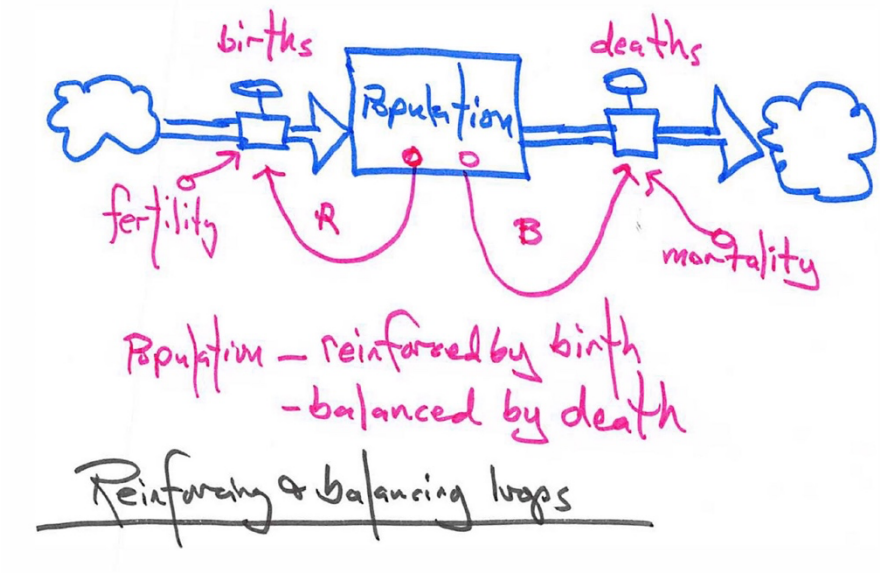

Figure 5. Examples of both balancing and reinforcing feedback loops.

So that balances out, and then mortality affects it.

So, these thin lines represent information. The population in this incident represents stock, which is the terminology used in systems analysis, and then the R represents a reinforcing, which could be positive or negative feedback loop.

In this case, more people are born, which means there are more people to have more babies. So there's a positive feedback loop. People are born, you have increased population, and depending on the fertility, that could lead to an increased rate of births, which would mean to increase population in this positive feedback loop.

That positive feedback look takes place, positive and negative, in female sexuality. So this represents flow. The clouds are where people start and where they go when not on this planet; we can leave that to the philosophers and theologians, but what we're talking about is the system or the flow after it starts to flow into the population.

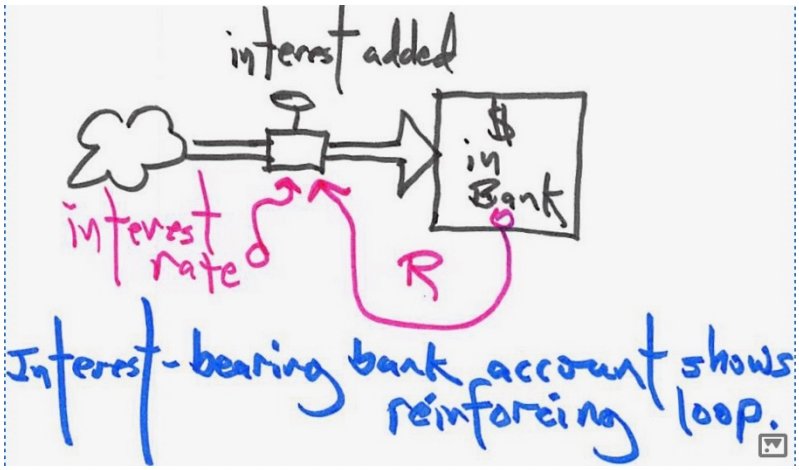

Figure 6. Example of a reinforcing feedback loop.

A more simplified look is like this, where you have a reinforcing feedback loop where money flows in in the form of interest and the more money in the bank, the more interest there is, depending on the interest rate.

So, adding more money meant that more interest gets added. There's money in the bank and then more interest gets added at a faster rate because there's more money and there's a positive reinforcing feedback loop. It could be negative as well.

If you look at the amount of money that Warren Buffet has, a huge percentage of it came in the last 10, 15 years because of this positive, reinforcing feedback loop.

Okay, a review of the feedback loops and how they work.

Now, let's go into the details about the neurotransmitters in the brain and how some on-label and off-label uses have to do with brain chemistry.

Brain Chemistry as Part of the Female Orgasm System

There are balancing feedback loops regarding brain chemistry that keep libido present but in control.

The following increases libido when levels are increased in the brain:

1. Sex steroids,
2. Dopamine,
3. Oxytocin,
4. Melanocortin,
5. Norepinephrine.

These decrease libido:

1. Serotonin,
2. Opioids,
3. Cannabinoids,
4. Prolactin.

Treatments (both medication and behavior) are based upon balancing those neurotransmitters within the brain.

Examples of Therapies that Change the Balance of the Brain Sex Neurotransmitters

Dopamine Agonist

My favorite off-label use of a *dopamine agonist* is Wellbutrin. I think 100 to 150 milligrams of long-acting Wellbutrin is about as good as it gets for helping depression and simultaneously helping with low libido. It is by far my preferred antidepressant for women for that reason.

Serotonin Antagonist

BuSpar is a serotonin antagonist, so it would inhibit the inhibitor and help both with depression and has been shown to help with sex drive.

Opioid Antagonist

The opioid antagonist is an interesting idea. When I think about opioids, I think it's worth remembering that those who use opioids, both by prescription or by abuse, really do see a significant drop in LH and FSH and, therefore, have decreased sex hormones. And I think there's probably other brain chemistry going on, but you must think about decreased LH and FSH when people are on opioids for pain control. So, using an antagonist, even though they were not on the opioids, can help with off-label use.

Norepinephrine

I have quite a few patients who say just using over-the-counter diet pills can be extremely sexually excitatory.

Of course, we have prescription diet pills (like Ritalin), which to me is a little bit pushing it because it puts you at risk with your medical board, but there is no doubt that excitatory amphetamine-type products (if you just go to Walmart and the diet pills that have ephedrine like products in them taken) 30 minutes or so before sexuality will improve libido.

Serotonin and dopamine can also change in relation to behavior (Young, 2007)

Oxytocin

Oxytocin is a lozenge or Sub-Q. It burns when you give it Sub-Q, but it gives this glowing sensation as if you already had an orgasm. And, of course, it is the love hormone that helps women bind with their children.

If you look in men's magazines, you'll see oxytocin-type sprays and colognes that are supposed to help women or encourage women to fall in love with you, and many millions have been made selling that idea in men's magazines.

But given sub-q, oxytocin is thought by some also to cause a stronger contraction when there's an orgasm. The additional glow is just like if you have a massage; there's this warm glow and relaxation that happens with a parasympathetic response, and that can be propagated by giving sub-q or sublingual oxytocin without the trouble of the massage. So that's an important and safe thing to do, a really safe product.

Those are some of the main hormones that come from the brain.

The Pituitary and Sex

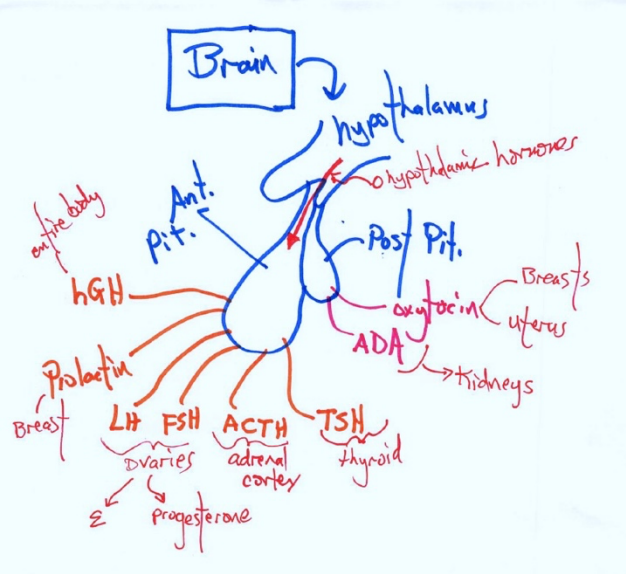

Figure 7. The principal hormones secreted by the pituitary gland.

The anterior pituitary secretes prolactin, which can decrease libido. Usually, there is a microadenoma, that does not require surgery, although it can be a macroadenoma. You diagnose the problem with a blood test.

Microadenomas with hyperprolactinemia are a clear example of how just one thing can be wrong in this balancing act and throw off the whole system. I probably average finding one person per year with this problem; not one per day, but one per year.

But when you make that diagnosis, it is life changing for your patient.

For example, a few years ago, the UPS driver who delivered locally, a very healthy young man complained to me that he had no libido and everything else was right about him: Testosterone levels were normal, he was in excellent shape from lifting boxes and walking all day, on no medications. But he had a high prolactin level and that's all it took to completely kill his sex drive.

Not Viagra, not a P-Shot® procedure, nothing else, I only give him Dostinex to drop his prolactin level, and he started having amazing sex with his wife.

Prolactin, of course, acts to cause breast milk production, and probably (with women) there is some survival mechanism that decreases libido to discourage a woman from getting pregnant again when she is breastfeeding the current baby, but prolactin kills sex drive in both men and women.

Some still think that prolactin should only be checked if other pituitary hormones are abnormal. But if you just make it a routine check for everyone who has decreased libido or anorgasmia, you'll find one to several per year, depending on how many patients you're seeing.

Often, there is not an associated surgical problem. The treatment is only just pill Dostinex twice a week to drop prolactin levels back to normal—and your patients love you for making this diagnosis and helping them back to great sex.

The anterior pituitary also makes growth hormone. Growth hormone has become politically (I think tragically) restricted over the past decade after the powers that be overreacted to the fact that people were writing too many prescriptions for growth hormone for bodybuilders.

There would have been a way to control that without reacting in such a way that it became risking jail time to for a physician to write a growth hormone prescription for someone with a true adult-onset growth hormone deficiency. So I've quit doing it.

I was involved in three different growth hormone research projects, and if you check IGF-1s and then do a formal stim test with IV arginine (30 grams over 30 minutes) and you watch for a rise in growth hormone, just like with a glucose tolerance test, you will find a deficiency in some of your patients. But the problem is writing the prescription, of course, risks jail time.

But growth hormone is not just about bones and muscle, as often illustrated in the textbooks. Like there's a receptor for thyroid on pretty much every tissue type, there is also one for growth hormone and IGF-1 (somatomedin C) is extremely important in both mental acuity, it helps lower cholesterol, and it's associated with depression and even agoraphobia when levels are low.

So it's an important hormone, and it has a huge thing to do; I've probably treated more adults with growth hormone than just about anybody you'll meet (over 300). And it has a huge effect on libido, but unfortunately, now you have to be, I think, outside the US or part of an IRB-approved study to prescribe it.

Other Pituitary Hormones

ACTH and TSH come from the anterior pituitary gland. We will cover thyroid hormones when we go into endocrinology.

Then the posterior pituitary would secrete vasopressin and oxytocin, which we already talked about, oxytocin influencing the breast and the uterus.

Those are the brain hormones and some of the things that can go wrong and some of the things that can be done to make them better.

Prescription Drugs to Affect the Brain and Sex

We have two FDA-approved drugs for women for sex, and they are both brain drugs. Glad to have them because we're starting with the brain because the brain is of course important, but there's no FDA-approved drug for the vagina except there's a DHEA, which to me is just a roundabout way of giving testosterone. So, I don't even really count DHEA cream.

Flibanserin

Flibanserin was a hard-fought battle to get approved (Addyi), and it was an antidepressant that did not work well as an antidepressant.

It is a serotonin agonist-antagonist, which would be a double, so it drops it.

Addyi gives an increase (on average) of one sexual encounter per month, and you must take it every day to achieve that one per month.

To me, it seems like it is a lot of trouble for one extra encounter per month, but I will guess one is better than nothing, and one extra over two would be doubling the amount of sex you're having. And obviously, a lot of people love it, and there are those who do better than the average as well.

There was a lot of concern about combining alcohol with flibanserin, with the synergy causing a profound and sudden hypotensive effect. I think that was probably overblown, and it's probably not as dangerous when it comes to dropping blood pressure as people think—but it stil must be considered as a possibility.

Of course, many people want to drink alcohol when having sex, so there is that downside.

Bremelanotide

And then the other FDA-approved drug to help women with sex, which also affects the brain is Vyleesi or bremelanotide. It offers the side effect of nausea.

If you, however, use it carefully and combine it sometimes with antiemetics, you can use it without becoming nauseated, but most definitely, it's a side effect that does not go well with libido.

But it does work, and I'm grateful we have these two drugs, but both are brain drugs, which is why I'm bringing them up in today's lesson.

Head Trauma and Pituitary Dysfunction

Head trauma that is not even severe enough to cause loss of consciousness can cause shearing forces on the stalk of the pituitary gland, causing disruption of circulation to the gland and knocking out some of the pituitary hormones, including growth hormone and TSH and LH, and FSH.

Usually, growth hormone is the first to go after head trauma.

In our current legal state, unfortunately, growth hormone is not something you can safely prescribe, but it is worth considering.

I found adult onset frequently when I was involved in a phase 4 study of Genotropin by testing people diagnosed with post-concussive syndrome: soldiers (of course a lot of women are soldiers) and athletes who suffered head trauma. It is worth considering that their post-concussive syndrome may have a component of just anterior pituitary hormone decrease.

As an example, I had a woman who came to see me, who was over 100 pounds overweight, and she had a low IGF-1.

She failed stim testing with iv arginine.

She'd been diagnosed with polycystic ovarian disease and was told that she would have to lose her 100 pounds to be able to get pregnant, which is to me a double bind because you cannot lose weight because you have polycystic ovarian disease (POD), but you are supposed to treat the POD by losing weight.

So, with this woman, I diagnosed her growth hormone deficiency (she failed stim testing, had symptoms, and a low IGF-1). I enrolled her in the phase four study for which I was a principal investigator. That IRB-approved study (sponsored by Pharmacia who eventually sold the drug to another

company), required more to make the diagnosis of growth hormone deficiency than was at the time required by Blue-Cross Blue Shield to make the diagnosis.[2]

I put her on Genotropin, she lost 100 pounds and came off two diabetes medications—and got pregnant.

Then, because of the history of diabetes, I sent her to the high-risk pregnancy department, OB-GYN department at the University of South Alabama (near my office) and asked them to keep her on her growth hormone for the first trimester, after which the placenta would make it.

The university diagnosed her with empty sella syndrome, stopped the growth hormone after her first trimester (as planned). Her bood sugars remained normal thought-out the pregnancy without any diabetes drugs.

She delivered a healthy baby boy.

Empty sella syndrome and head trauma—they both do happen. It's not something you see every week, but if you watch for it, you'll find a low IGF-1 and make the diagnosis; watch for it in the morbidly obese with type II diabetes. If you find it and if you have the courage to write the prescription for growth hormone, you will dramatically change people's lives for the better.

Next lesson, we will discuss the anatomy and function of the clitoris in relation the the female orgasm system.

References

Urology recommends that urologists become therapists because “most instances of acquired impotence are psychogenic.” Now, history repeats itself—both FDA-approved drugs intended to help women with sexual dysfunction are psych drugs (they only affect brain chemistry, not the female genitalia).

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Brain chemistry must function properly for the female orgasm system to function properly.

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[2] Blue-Cross Blue Shield of Alabama audited me in September 2003 because my patients requiring growth hormone replacement were costing them too much money. They changed their requirements for the drug the following month: they started requiring more than one pituitary hormone abnormality and failure of iv insulin stim testing (a very dangerous test that risks stroke and heart attack). Almost all of my patients lost funding for their growth hormone replacement.

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