>> Steve Langjahr: It's November 28 and it's still 2016. This is sort of some unfinished business. We left you with the thyroid gland and so next on our agenda, Roman numeral VI, the adrenal glands, specifically the adrenal cortex. You know the location of the adrenal gland. It sits on top of the kidney. In fact, today the adrenal gland is more often called the suprarenal gland. But never mind. The cortex is what we're attending to now. It's that thin layer which surrounds the adrenal medulla. So let's enumerate the hormones that are produced here. And chemically speaking, they're all steroids. That means they're fat-soluble hormones. The list is as follows. The first category of steroids produced here are those that are referred to generically as mineralocorticoids. A lengthy word, but let's dissect it. At the end of the word, we see -oid, o-i-d, which is a reference to the fact that these are what?

>> Steroids.

>> Steve Langjahr: And then we have mineralo which references minerals. And we see corti which is a reference to the adrenal cortex. So even though it might be cumbersome, the word makes sense. These are steroids produced by the adrenal cortex, which apparently have something to do with mineral adjustments, specifically as we'll see, sodium and potassium. The next category of steroids that are produced and secreted here are called glucocorticoids. This makes reference to glucose and so as we'll see, these hormones adjust and maintain and support blood sugar among other things. And the third family of steroids also produced here are androgens. The word andro refers to men, m-e-n. And so these are hormones that are essentially male sex hormones produced even in the female as we'll see. So let's now list the actions of these hormones in simplistic terms. First, you already know that aldosterone is a mineralocorticoid. It is the most important of the mineralocorticoids. Therefore you know what its target is, you know what its actions are. It basically supports the reabsorption of sodium chloride and water. Also, it leads to the secretion – that means the loss – of potassium in the urine. So very simply, aldosterone targets the nephron. It promotes sodium retention and it's obviously concerned with the elimination of potassium. Essentially this is controlled as you know, mostly by the renin angiotensin mechanism. New, at least new to us here, are the glucocorticoids represented by cortisol, also known medically as hydrocortisone. Cortisol has effects which first target protein and cause proteolysis. What's that mean, proteolysis? The breakdown of?

>> Protein.

>> Steve Langjahr: Protein. And that makes available free amino acids. That is, it tends to raise amino acid concentrations in the blood. It also breaks down fat, and the word for that, lipolysis. So breaking down fat releases free fatty acids and glycerol. The latter can be transformed into glucose. And so you see the basis for this description. We said cortisol was what? A glucocorticoid because it helps to promote raised blood sugar by virtue of lipolysis. It also of course makes available fatty acids which represent an alternative fuel supply. What I'm saying is, can some cells use and get by on fatty acids? Yes. So essentially cortisol helps

to provide for these substrates including fatty acids and glycerol. However, by far the most important value of this hormone, at least medically speaking, is its contribution to medicine. Because it's used very widely as an anti-inflammatory agent. It can be injected into joints, it can be more or less made or prepared as a cream or an ointment. And it's used to reduce skin inflammation, whether it's eczema or psoriasis or just a mosquito bite. So its widely used as an anti-inflammatory drug. And that sounds good and it is an amazing compound, but taken in excess, especially orally, it's dangerous because it has what effect on the immune system? Immunosuppression. So actually you can buy this drug in very low concentrations over the counter without a prescription. And I will bet that you have this in your medicine chest at home as a cream or an ointment. But it's not available orally or by injection without a prescription, because it's dangerous. It leads to what? Immunosuppression. So it's useful primarily as an anti-inflammatory agent, because it reduces capillary permeability. But aside from that, you can see that it's helpful in supporting blood sugar, and it does so at the expense of what? What is sacrificed in order to maintain blood sugar are fats and proteins. And so it is catabolic in that regard. Next, a word about androgens. Androgens are male sex hormones represented mainly and mostly by this one which is well known, testosterone. Where does most testosterone come from in men? Their testes. But do women make some testosterone? Apparently yes. And they do so from their adrenal cortex. Its value is to stimulate protein synthesis, therefore it's an anabolic hormone, not a catabolic hormone. In fact, I'm quite sure you've heard the expression anabolic steroids. And those are really referring to testosterone which are used and abused by who for what purpose?

>> Athletes.

>> Steve Langjahr: Who buys on the black market anabolic steroids? Athletes, bodybuilders, et cetera. Don't get me wrong, not all athletes, not all bodybuilders. But you know how it goes. So it is valuable because it leads to protein synthesis, which means in essence muscle development. It builds muscle and also supports the growth and strength of the skeleton. Now in women and in men too, it has an effect on the brain. It promotes sex drive, AKA libido. And so if a man complains of low sex drive or if a woman complains of low libido, what's prescribed or often given? Testosterone. It just has to be managed. You don't want to overdose on testosterone, especially if you're a woman. So let's get away from that and focus on control of secretion. Remember, we're talking about not the adrenal medulla, the adrenal cortex. And you might recall a hormone produced by the pituitary with this acronym ACTH, also known as ACSH. But at least the words adrenal corticotropic hormone suggest that ACTH targets the adrenal cortex. But incidentally, specifically and namely the glucocorticoids and the androgens. It has little effect on mineralocorticoids because those are controlled as you know by the renin angiotensin mechanism. So mineralocorticoids are outside the sensitivity to ACTH. Mineralocorticoids are released in response to changes in sodium levels or in potassium levels. Glucocorticoids are sensitive to ACTH. And this tends to be triggered by stress. Stress meaning

physical stress or emotional stress. Physical stress can be trauma. It can be an infection. Emotional stress would be taking physiology for instance. So all of these lead to high levels of cortisol which is the premier glucocorticoid. In fact, for that reason, cortisol is often described as the body's main stress hormone, because it is connected to and released in response to stress. It might seem in appropriate or without purpose, but as you look back, what does cortisol do? It breaks down protein and it breaks down fat and makes available amino acids to build and repair injured tissue. And it also makes available glucose or fatty acids which provides a substrate for energy. So even though cortisol is basically catabolic, its value in stress is that it helps support the body, that is a response to injury, a response to healing, a response to any kind of stress. And then there are androgens, which are of course mainly represented by testosterone. This also seems to be controlled by ACTH and is more or less kept in check, that is kept in bounds by the limits of feedback. In other words, more of these are released when the hormones dwindle, and less are released when the hormones are secreted. So as has been our pattern, once we've identified the hormones, the actions and the manner of control, we want to look now at what factors can upset the secretion of these hormones. What are some of the disorders which are famous or likely to be encountered in a clinical setting? So typically they break out into two categories, either too much or too little. And too little, generically, is called hyposecretion or hypofunction. And naturally, in this context it might affect one or all three of these hormones. And the first classic case of hypofunctioning with respect to the adrenal cortex is a condition called Addison's disease. Discovered in the 1800's by guess who?

>> Addison.

>> Steve Langjahr: Addison. It's basically featuring low levels of aldosterone and/or low levels of cortisol. Androgens are usually not part of this clinical picture. So the symptoms we're about to list mainly are the result of low levels of aldosterone and/or low levels of cortisol. And here they are. Naturally there's going to be a loss of sodium, and with it a loss of water. And with that, the loss of chloride. The water loss alone will lead to low CO. What's that? Cardiac output. And low BP, low blood pressure. This tends to reduce one's tolerance or capacity for exercise, because clearly to exercise you need a good cardiac output and healthy blood pressure. Very often, it's also linked to hypoglycemia. What's that mean? Hypoglycemia, low blood sugar. And that is related to the low levels of cortisol. There also may be weight loss, but it's usually not fat loss. It's water loss. If you lose water, will you lose weight? Yes. So this weight loss is mainly dehydration. There may also be high levels of blood K. What's that? Blood potassium. Again, related to the absence or shortage of aldosterone. The flip side of this story is not hypo but hyperfunctioning. This was described by Harvey Cushing and so in his honor it's called Cushing disease or Cushing syndrome. Usually, mostly, it's mainly too much of cortisol. Aldosterone is not in this picture. Neither is testosterone. Therefore, the biggest problem with this is just too much cortisol. And if you think about what cortisol does, that's going to lead to hyper – not hypo – hyperglycemia. What's that?

>> High blood sugar.

>> Steve Langjahr: High blood sugar. And at first of course, if you have high blood sugar, what would be the first thing that would come to mind to a clinician, to a doctor, to a practitioner? High blood sugar?

>> Diabetes.

>> Steve Langjahr: Diabetes. But it may in this case be something totally unrelated, i.e. Cushing disease. And easy to spot because when it happens, it produces very characteristic changes, here seen in a case history. This is an adult woman who made her living as a model, but then she developed Cushing syndrome or Cushing disease. And it leads to what? Protein and fat what? Catabolism. Which tends to lead to weight loss. But strangely, and paradoxically, the fat tends to redistribute and develop between the shoulder blades and creates this characteristic hump on the back, which is called, not very flatteringly, the buffalo hump. And it also causes a lot of fat to be deposited in the face. So you see the transformation there. So it's easy to spot based on the clinical presentation. But aside from that, the big impact is on the immune system. Because remember, too much cortisol causes immunosuppression. So this is dangerous of course in that way especially. Now as an isolated syndrome, it's quite possible for there to be too much androgen by itself. And if that happens, it would go totally unnoticed in a man because what are we talking about? What is the androgen that we've mentioned by name? So if men have too much testosterone, that's great. They just get more dates and they are more popular as a rule. But if a woman gets too much testosterone, that's not very pretty because the woman now is shaving twice a day and has got a deeper voice and essentially not a welcome thing. It's something that is called virilism as it occurs in a female. And typically would capture the attention of the female if she had this condition. So let's leave the adrenal cortex and move back actually to the pituitary gland. Because we left you with a list that we said we would revisit. And one of the hormones that makes perfect sense by name is growth hormone. Growth hormone is abbreviated hGH, human growth hormone. It's a protein, a bona fide protein, a water-soluble hormone. And its actions are somewhat logical, somewhat paradoxical. First, promotes what?

>> Lipolysis.

>> Steve Langjahr: Now that's paradoxical, because what does that mean, lipolysis?

>> Breakdown of fat.

>> Steve Langjahr: And breakdown of fat doesn't sound like growth, does it? But what do you get when you break down triglyceride? You get fatty acids and glycerol. And glycerol can be converted to glucose. And are fatty acids and glucose useful in cell division, in growth and repair of tissue? Yes. So even though this is catabolic in that regard, it does provide an energy source for growth, and that makes some sense. More to the point, growth hormone

promotes – it stimulates the uptake of what? Amino acids. And what are amino acids used for by all cells? To make protein. And what cells have a real appetite for amino acids are muscle and bone. So is this a bone building? Is it a muscle builder? Yes. Do bodybuilders buy on the black market hGH? Can it be had? Yes. And would this enhance their physique? Would it build their muscle? Absolutely. Because it stimulates protein synthesis. That means actin, myosin and the proteins, collagen and so forth that are important in skeletal growth. However, it's not without some risk as we'll see. But let's postpone that for now. Growth hormone also blocks the entry of glucose into cells, which is somewhat paradoxical. But it therefore makes glucose more abundant where? If we block its entry into cells, then it's going to build up in the blood and be more available than for the brain, which as you know has a huge appetite for glucose. The control of this hormone is not entirely related to youth. In other words, it's easy to assume that this hormone would be important in children and not so important in adults. But that's not exactly true. Its release is under the influence of GHRH, growth hormone releasing hormone. And it's actually promoted in what? Sleep and in periods of low blood sugar, and with exercise and once again our friend stress. So people who exercise obviously have higher levels of growth hormone, which would support the development of what? Muscle and bone. So these ideas kind of come together and make some sense in that context. Disorders are fairly easy to imagine. That is, we have once again hyper or hyposecretion. Hyposecretion means too little growth hormone. And if it occurs in a youngster, it stunts their growth. It stops them from reaching their actual genetic potential in terms of height. And what do you call people who are short? Well, short people I guess. But no offense intended, they're called dwarfs. And of course you know what I'm talking about. This is called pituitary dwarfism. Incidentally, this is not what you see on TV if you're thinking about little people and – what was her name? Terra Jole who was recently on Dancing with the Stars. None of you guys watch that show. Okay. But those people, if you think about them, they have regular bodies, regular heads, but very short what? Limbs. And that's not pituitary dwarfism. That's something called achondroplasia which has to do with the epiphyseal growth plate. But are there people who are disproportionately – that is of normal proportion but small? Yes, they're called what? Pituitary dwarfs. And the opposite of that is a giant. It's called just that, giganticism. And these people usually find employment in the sports or entertainment world, right? Because they're good at dropping basketballs into nets and that sort of thing. So that's all well and good. But what if you were to take growth hormone as an adult right now? Would you suddenly get taller? The answer?

>> No.

>> Steve Langjahr: No. Because your epiphysis and your diaphysis have fused and there's now way for the skeleton now to elongate. What happens instead is that the skeleton becomes thicker, heavier, coarser. The fingers change quite dramatically, becoming thicker and very large. And also there's hyperglycemia as a symptom. That's what? High blood sugar. Basically this condition is

called acromegaly. It's most obvious in females because their femininity is more or less transformed. They start looking more manly, again, because changes in the hands and feet especially. Just before we leave, we can comment again, how do you treat underactive endocrine function? Underactive, you just give them what? The hormone. Either by injection or orally as the case may be. If the gland is too active, then you have to destroy the source of that hormone. That's tricky here because where is this hormone coming from? It's coming from the pituitary. Are there other hormones that are produced there as well? So you just can't blow away the pituitary. Yes, you might effectively get rid of this problem, if you even think of it as a problem. But more importantly, you're going to bring down other valuable hormones. So very often hyposecretion is easy to treat. Hypersecretion, not so easy to treat. And before we leave the endocrine glands and move on to reproductive physiology, one more deserves our attention. It's called the parathyroid, which you might recall from anatomy is actually rather difficult to see, a small group of cells or tissues located behind the thyroid. This gland produces a peptide, a small protein. It's called parathyroid hormone, also called parathyrmone. Its actions are quire straightforward, very simple. It maintains or helps to support normal calcium and phosphate ratios in the blood. So what are its targets? What sites would contribute to or help maintain calcium and phosphorous levels? Well, first obviously the bone. So this action, this hormone targets bone and helps to release calcium from bone. That's easy to say, easy to memorize, but where does this calcium go? It goes into the blood and that would raise calcium, which in itself is not necessarily a good thing. Except in which gender at which time? Okay, females during pregnancy. Why would high levels of calcium be welcome there? Not for the mother, but for the developing fetus. Because he or she needs calcium. So this hormone is valuable in women during pregnancy. In effect, it steals calcium from the mother's skeleton and makes it available for the developing skeleton of the fetus. In the kidney, it also supports the reabsorption of calcium and it has a similar effect along the GI tract. So if someone were to summarize the targets of this hormone, first it targets bone, it targets the small intestine and it targets the kidney, all serving to raise or elevate calcium levels in the blood. Primarily useful again in women during pregnancy. And with that said, what factors would stimulate the release of this hormone or control its secretion? Well, not surprisingly, it responds directly to blood calcium levels. So if calcium levels are falling for any reason, and mainly and certainly commonly because people are not eating enough what?

>> Calcium.

>> Steve Langjahr: Do we eat enough calcium as kids? We do, because we tend to eat ice cream and dairy products and so forth. What happens when we get older? No dairy products. We switch from milk to Dr. Pepper. And is calcium abundant in Pepsi or Dr. Pepper? So what's my point? If there is low blood calcium, this hormone will be secreted and therefore rob what tissue of its calcium?

>> Bone.

>> Steve Langjahr: Bone is going to suffer as a result. And so certainly that's necessary to support calcium. Think about it, what is calcium valuable for? It's valuable in electrolyte and especially sodium and potassium equilibrium potentials. It's also important you know in blood coagulation. So maintaining blood calcium is an important issue, and this hormone helps to do just that. So what would be some of the fallout from dysfunction of the parathyroid? If you had too much of this hormone, that's called hypersecretion. Too little is called what? Too little is called hyposecretion. This leads to very low levels, lethal levels of calcium. Because as you know, low levels of calcium tend to promote sodium influx along axons. Therefore it depolarizes the resting potential, therefore leads to what? Leads to increases in neuromuscular excitability. In a word, what translates is the T word. What's the T word? Tetany. And what muscle can you not afford to have tetanize?

>> Diaphragm.

>> Steve Langjahr: Diaphragm. So this leads to respiratory arrest and is of course lethal. How would you treat this disease? You might think, well, if they're not secreting this hormone, then the obvious thing to do would be to give them what? The hormone. And that would work, but this is expensive stuff. So a much easier approach to this is not to replace the hormone. I mean, after all, the problem is what? Low blood calcium. Can we go right to the source and fix that without even worrying about the hormone? Yeah. So calcium supplements would be sufficient to forestall or secrete hyposecretion of this hormone. It also leads to high plasma phosphate which is really no big deal but worthy of mention because we said earlier that this hormone maintains the proper ratio of these two electrolytes. Hypersecretion, not a big deal, because essentially this would lead to high blood calcium which in itself is not life threatening. But it does after all get this calcium from where? I mean, if the calcium in the blood is high, it had to be stolen from where?

>> Bone.

>> Steve Langjahr: And so this is going to demineralize the bone. The bone will not be brittle. The bone will be the opposite of brittle. What do you call bone that bends? It's flexible or pliable. And this leads to bowleggedness, also something called osteomyelitia, which you might recall from anatomy. It also leads to muscle weakness, again because of the high levels of calcium. And this high levels of calcium can actually be filtered. And now the urine has high calcium, so high in fact that the calcium may precipitate and form rocks. What do you call rocks of calcium as they develop in a kidney?

>> Kidney stones.

>> Steve Langjahr: Kidney stones which are painful and problematic if they occur. Notice I have a question mark because we're making it clear that this doesn't always cause kidney stones, but it might promote or otherwise be con-

nected with some form of kidney stones. So I know that's been a lot of information, but it is mainly memorization. Memorization of ideas. Again, when any hormone is mentioned, you need to know its actions. You need to know the targets that are affected by it. And also how it's controlled. But specifically and most importantly clinically, what happens if we have too much? What happens if we have too little? Those are things that would obviously be addressed in a definition. That is, what's the physiological significance of PTH? Its significance is that it can change and upset neuromuscular excitability. And also on the flip side lead to changes in muscle status and bone status. So I know this is an abrupt transition now, but it's time to turn away from endocrine issues directly and start to speak for the rest of today and also Wednesday and even Monday about reproductive physiology. And this is logically and obviously connected to the endocrine system. Because are there hormones that influence and determine male reproductive success? Of course. So it's a good and natural segue between endocrine and now reproductive physiology. So let's knock out the male in the time we have left. We may or may not finish, but we'll give it a go. We know that in men the gonads are called the testes. And you know men have two of them, at least theoretically. And you know that these are outside the body in the scrotum. As far as our concern, we're not going to dwell on the anatomy except as it supports and makes possible the functionality. But let's get down to it. The testes produce sperm, at least in adulthood. And those represent the male gametes. Do males produce sperm throughout their life? It's not a trick question. Do eight-year-old boys produce sperm? Luckily not. So this is an adult onset situation. And once it begins, it never shuts down. Men even in their 80's and 90's still will produce some sperm. And to make that possible, there must be the supportive hormone, the steroid produced also by the testes which you know is called testosterone. In short, without testosterone, sperm cannot be synthesized. So these are essentially linked together. No testosterone, no sperm. So when it comes to the factors or functionality of the male reproductive system, there are two issues that we have to understand and describe. The first is making the sperm. The second is delivering the sperm. So manufacture and deliver. What is the word for manufacturing sperm? Spermatogenesis. Spermatogenesis doesn't begin until puberty, and incidentally is dependent on gonadotropins from the pituitary, namely as we'll see later today, FSH backed up also by ICSH. These are the important pituitary gonadotropins. Once they arrive, once these hormones are available, then and only then spermatogenesis can begin. This process of course occurs in the testes and is going to begin with a cell which is a nondescript precursor cell. You can barely read here. And that is named a spermatogonia which is rather boring-looking. That is, doesn't resemble anything particularly interesting or unique. The important thing about these stem cells if you want is that they are normal in their chromosomal count. They have the diploid number which is 46. Now sexual reproduction, you learned in biology, is not done with somatic cells. It's done with sex cells. And so the process we're about to describe is not mitosis, but miosis. And that reduces the chromosome count from 46 down to half, which is what? Half of 46 is 23. We call that transformation diploid

down to haploid. So as you look to this chart – and your textbook has a better version – we see that early on there is simply mitotic division followed then by miosis, whereas a single cell, this cell, is going to be transformed into four. And this reduces the chromosomal count from 46 to what? 23. Along the way, these cells develop characteristic appearance, which includes towards the final stages the acquisition of a flagella or a tail. Which makes these cells very motile, very self-propelling as you know. So this transformation is shown diagrammatically here. And the chromosomal count which starts at 46 is reduced to 23. You also know from biology that among those chromosomes there are the so-called sex chromosomes which contain the genes that determine gender or sex. You may recall from biology that those genes for a female are on the X chromosome and those genes which confer or otherwise produce a male are on the Y chromosome. Notice of the sperm that are made, what percentage carry then the feminine genes? Half. What percentage contain the Y chromosome? 50%. So you learned this in biology. Which parent determines the sex of their offspring?

>> Male.

>> Steve Langjahr: It's the male. And so it's all a matter of chance. If a sperm that carries the X chromosome is successful, then the child will be a girl. If instead it's carrying a Y chromosome, the child will be a male. And what is the statistical expectation in that regard? In other words, in terms of the population, at least theoretically 50% should be what? Male. And 50% should be female. Now in any given family that's just a coin toss. Is it possible for a family of four to have all girls or all boys? Yeah. But certainly on a global scale, there should be about 50% boys born and about 50% girls born. This is all a matter of luck or chance, that is remember, it's the sperm that actually reaches and fertilizes the female ovum which will determine that sex. So to restate this, this process is what? Spermatogenesis. And it's dependent on these hormones from the pituitary which have been called and are known to you as gonadotropins. And without those hormones, the testes will not respond. And of course, to remind you, are these hormones present in an eight-year-old boy? No. But once they're released, then spermatogenesis is a lifelong process which generates millions of sperm every day. Now the vehicle, that is the solution in which sperm are mixed and actually dispersed is something you know of, semen. Semen is the liquid vehicle for sperm conveyance. And this is not produced by the testes. The testes produce very little in the way of fluid. Their main contribution are the sex cells, namely the sperm. But where then does the semen come from? What are the accessory organs that contribute to semen? You know them by the name prostate, seminal vesicles and to a lesser extent a tiny pair of exocrine glands called the bulbourethral glands. Anyway, semen typically would amount to maybe 2-5 milliliters per ejaculate. And in that small volume there would be what? Wow, that's a staggering number. 50-150 million sperm per what? Per milliliter. So do that math and you would be stunned by the overkill here. What do I mean? How many sperm does it take to fertilize an egg? One. But why these huge numbers? Well I'm sure you know the answer to that. Massive mortality. What does that mean? The sperm are

delivered to the vagina, but do they all make it to the oviduct? No. Some go up the wrong oviduct, you know, just blind luck that they go up an empty tube. Some never make it into the uterus. They dribble out the vagina or whatnot. So my point is, these numbers are needed. In fact, at least clinically, if a man has a sperm concentration less than 20 million per mL, they're declared infertile. Infertile with 20 million sperm per what? Per milliliter. So when a family is having trouble conceiving a child, is it always automatically the woman's fault?

>> No.

>> Steve Langjahr: No. So what should the man do? The man should give up some semen, let's analyze it. Let's make sure these guys are actually swimming and let's make sure that there are sufficient numbers to get the job done. And if not, then there's your problem. Remedies would have to be investigated. But my point is these numbers are necessary because of the large mortality that occurs along the way to the oviduct. Now what about semen? Obviously it's an aqueous-based solution, a water-based solution. But if you measure its pH, it actually measures out at 7.4 which you know is on the alkaline side, right? So very different from urine in that regard. And the reason it's alkaline is because of the presence of bicarbonate, but that's not really a reason. That's more of an observation. Why should it be alkaline? Remember, semen's going to be going through what tube on its final hurdle?

>> Urethra.

>> Steve Langjahr: The urethra. And what normally goes through the male urethra is?

>> Urine.

>> Steve Langjahr: And urine is normally acidic. And acidity is very caustic, very dangerous to sperm. In other words, it kills sperm. So the bicarbonate levels here neutralize the urethra and there fore minimize the damage or threat or the injury to sperm as they pass through. And where after all does the semen come from? Most of it comes from the seminal vesicles which are two bilateral structures just behind the bladder, as you know. And a lesser extent the prostate which is nestled under the bladder surrounding the first segment of the urethra as you probably also know. Other ingredients in semen are kind of curious and unexpected. One is a monosaccharide called fructose. And so the question is, why should semen be sweet? I mean, what's the function of the sugar in semen? It appears to be necessary because are sperm avid swimmers? And what's it take to move these flagella? ATP. Do you imagine there's much room for glucose in the tiny warhead of each of these sperm? No. So what's the question? Where does the sperm motility find support? It's in the available monosaccharide called fructose. So fructose provides the substrate for ATP production which is necessary for sperm movement. Also found in semen are compounds called prostaglandins. You recall we mentioned those early in the course as mediators of pain. Histamines, brachinine, prostaglandins. But actually there are many

kinds of prostaglandins. And if you look at the word, where do you suppose that word came from? Where do you suppose prostaglandins were first discovered?

>> Prostate.

>> Steve Langjahr: In the prostate. So these are different from the prostaglandins we've discussed. These are smooth muscle stimulants. And what smooth muscle would these prostaglandins make contact with? And to what benefit would that be? I mean, after all, the vagina is smooth muscle, the uterus is smooth muscle. So this helps, we assume, to bring about motility of the female as well as parts of the male reproductive tract. And therefore may help to coax or bring together the male and female gamete. It's quite uncertain as to the importance of these prostaglandins, but nevertheless they are there. And even more bizarre at first is this, which is what? Fibrinogen. We know that's found in blood. We know that normally comes from the liver. And we know that that's important in converting to the insoluble protein called fibrin. And that's normally associated with what process?

>> Clotting.

>> Steve Langjahr: Clotting. Now don't confuse this. This is not blood. This is what?

>> Semen.

>> Steve Langjahr: But nevertheless, we're asking the question, can semen clot? Can this fibrinogen be converted to fibrin? The answer is yes. So semen which is liquid at least naturally and in the beginning, once it's ejaculated into the vagina, this fibrinogen is converted to fibrin and that converts this liquid semen into a gel. G-e-l. And the alleged advantage of that is that now this is less watery and therefore less likely to do what? If semen were water like then it would just what? Roll out the vagina and therefore not serve any purpose. So this coagulation may serve to hold the semen where it should be held, namely up against the cervix so that its sperm uptake can be facilitated. And here's a surprise too. There are also compounds called seminal plasmids which are actually antibiotics, that is kill bacteria. Why would you want to kill bacteria? Does semen have any bacteria in it? No. But does the vagina have bacteria in it? Yes. And so this is more or less a protective measure which prevents perhaps the uptake of bacteria into the female reproductive tract. Let's be clear. Is the vagina loaded with bacteria? Yes. Is the uterus loaded with bacteria? No. So would you want bacteria to move from the vagina into the uterus? No. And this may help actually minimize that possibility. So there you have it. That page was all about spermatogenesis. The next issue which we said is expected and necessary is the delivery of sperm. Which obviously requires sexual activity which you're well familiar with. But the general name of what is accomplished here is called insemination. So what we're about to describe is natural insemination, which is actually a two-stage process that begins and must begin with an erection. That is, we need an organ of copulation which is

turgent or rigid enough to serve as an organ of copulation. And is the penis of a male normally flaccid or erect?

>> Flaccid.

>> Steve Langjahr: I'm here to say it's normally flaccid. Can it become erect? Yes. And that process is a reflex actually. And if you think about it, what are spinal reflexes all about? What are the minimum components that you have to have for successful reflex? Do you need a receptor?

>> Yes.

>> Steve Langjahr: Yes. Do you need a sensory nerve? Yes. Do you need an intact spinal cord? Yes. Do you need motor nerves? Do you need some sort of effector? So believe it or not, an erection is fundamentally a reflex. And even though it doesn't require the brain, it is often enhanced by the brain or inhibited by the brain in ways that we'll mention. So here's a very crude wiring diagram of what's going on here. The penis is clearly obvious and the scrotum is there just for reference. The lower spinal cord is where this reflex will be passed. And so let's begin at the beginning. The usual or a usual stimulus is contact with the glands, that is some contact with the tip of the penis. This can be manual or otherwise. And so what are there that respond to touch? What are these receptors in the penis? Well, they're called mechanoreceptors. And this initiates action potentials which travel up sensory nerves, making their way to the spinal cord. So step one, excitation of penile mechanoreceptors. This brings about an increased frequency of action potentials along sensory nerve pathways to the spinal cord. And item three is an autonomic response through autonomic motor nerves that then takes place. Item three, what is it inhibition of? Sympathetic and excitation of parasympathetic fibers to the arterials that supply blood to the copora cavernosa as you may recall. In case you're a little rusty on that anatomy, the penis is basically a structure which contains two vascular sinuses. The one above or dorsally are called the copora cavernosa. The one below is the corpus spongiosum. Do these normally contain blood? No. Can they fill with blood? Yes. And what does it take to increase blood flow into any organ? Are we going to dilate or constrict?

>> Dilate.

>> Steve Langjahr: Dilate. And that is made possible by inhibition of sympathetic fibers. But in this location, a curious and rather unique departure from normal vasculature, we did say in the last unit that most arterials only have what? Most arterials are only innervated by sympathetic. They didn't have what?

>> Parasympathetic.

>> Steve Langjahr: Parasympathetic. Here's the exception. These arterials also have parasympathetic, but they're not the run of the mill because they don't have acetylcholine. They use what? Non-cholinergic. Actually, instead of

acetylcholine, these receptors respond to nitric oxide. Which was quite a stunning discovery when it was made, because up until that time, most parasympathetic responses were mediated by what? Acetylcholine. And it was assumed that all parasympathetic were mediated by acetylcholine. Then they discovered these which are not triggered by acetylcholine but instead by what? Nitric oxide. Quite unexpected. And so although that's a fact, the question might be what advantage is this? I think it's pretty clear that what we want to achieve here is widespread vaso-what?

>> Dilation.

>> Steve Langjahr: And just relaxing the sympathetic would bring about some vasodilation, but we really need more vasodilation to improve blood flow into the penis. And that seems to be made possible not by reduction of sympathetic, but by stimulation of what? These non-cholinergic parasympathetic. And so around about 1998, quite by accident, a compound was discovered which improves the production of this gas. What is it? Nitric oxide. And so that pill – and I know you know the name – has been quite popular to say the least. And for what treatment or for what call it dysfunction is Viagra used for? It's to promote what? This – what is this? This massive item here, massive penile arterial dilation. In other words, Viagra is useful in treating ED. What's ED? Erectile dysfunction, which we used to call impotence. But everybody started squirming with that and it just didn't sit right. So we made it a little less assaulting. It's called what? Erectile dysfunction. Anyway, let's be clear, Viagra doesn't cause an erection. It simply promotes penile arterial what? Dilation. Doesn't cause it, but it helps it. And this still has to be triggered by some extraneous factor, whether it's stimulation of the mechanoreceptors or what. Anyway, the net result apart from the arterial dilation is that blood fills these sinuses. And what happens to a kitchen sponge when you put it into water? It gets big, right? It doesn't get stiff, but it does get big. And so the size of these sinuses will increase and the girth or diameter of the penis will enlarge. But here's the trick. That is, when these sinuses swell, they tend to pinch. They tend to literally squeeze shut veins which normally carry blood where? Out of the penis. So if we have all of this blood coming into the penis but very little blood going out, then what happens to the blood pressure in the penis? What happens to the penis? Well lit becomes upright. That is, turgid and that then is the completion of this so-called reflex. Notice the asterisk here, because this response, even though it might in many cases be triggered by tactile contact with the tip of the penis, is also easily or at least conceivably achieved by mental changes. Can a man develop an erection by thinking erotic thoughts or watching pornography or whatever? Of course. And so this reflex is influenced – what's this say? Negative and what? That means it can be promoted or what? Inhibited by mental status, thoughts, that is erotic thoughts or thoughts of performance anxiety or whatever. And so that is the basis usually incidentally of a normal erection or the inability to achieve an erection. In other words, sex begins and ends where? In the brain. This is just plumbing which makes it all happen or not, as the case may be. And can drugs influence this response?

Naturally, because many drugs that we might mention can affect the mental status of the individual, that is relieve anxiety or cause anxiety. And also drugs that might act on blood vessels, not the least of which is Viagra or Cialis, et cetera, which promote vasodilation by improving the parasympathetic response. So fundamentally, this is a reflex. In other words, does the brain need to be involved? No. Can it be involved? Yes. And with that said, what about a paraplegic? A paraplegic might have total severance at this level. Would a paraplegic be able to feel any contact with their genitalia? No. But would a paraplegic be able to achieve an erection nonetheless? Yes. That wouldn't be mentally provoked but rather some sort of what? Physical contact with the penis. So what have I said? Can a paraplegic achieve an erection? Yes. Can a paraplegic make sperm? Yes. And the next step of course is ejaculation. And is that possible? Yes. So can a paraplegic engage in some form of sexual activity and bring about impregnation of a significant other? Sure. So we want to think of paraplegics not as incapacitated in this regard. However, they do lack what obvious benefit or obvious aspect of sex that other folks enjoy, is what? The physical sensory thrill of this activity. So that part is missing, quite sadly. But moving from an erection, the next stage which typically follows and indeed has to be preceded by an erection, is ejaculation. Ejaculation is the emission of semen and presumably sperm – although not always. Is it possible to ejaculate with no sperm in there? What's the usual reason that semen wouldn't have any sperm?

>> Infertility?

>> Steve Langjahr: Well yes. But I'm thinking of a surgical option that many men exercise. Yeah, their thing is snipped, yeah. From anatomy, recall that that tube is called the vas deferens. And the clipping of the vas is called vasectomy. Do men who have had a vasectomy still get an erection? Yes. Do they still ejaculate? Yes. But is there any sperm in there? No. All right. That sounds good to me. All right, so anyway, ejaculation has to be preceded by an erection. And it's a rather rapid sequence of events. The first phase occurs sooner or later, that is a crescendo or buildup of sympathetic impulses again due to penile thrusting or penile activity of one kind or another. This causes the genital ducts to contract. After all, these ducts are made of smooth muscle. And the glands that we're referencing here are the prostate and the seminal vesicles. Basically this brings sperm up from the testes and brings these cells into contact with semen. Semen from what source? Where's the semen coming from? Prostate and seminal vesicles. This mixing if you will occurs inside the prostate at a location called the ejaculatory duct. And so here's where the sperm meet what for the first time? Sperm meet the semen. And the mixing is within a second or two. Followed unpreventably, in other words automatically. If you get phase one, phase two happens without any way to stop it, phase two is the rather propulsive and significant contraction of skeletal muscle which of course occurs and brings about a wave of seminal release which takes place over some number of seconds. So that's all the story of insemination. Let's talk about the hormones that make all of this happen or even possible. And so we leave the male reproductive or-

gans for the more lofty location, namely the pituitary. What does the pituitary release that has anything to do with the performance of male sexual activity? Certainly FSH and the other one called ICSH. In females, that same hormone is called LH, luteinizing hormone. FSH is a strange name because literally it means what? Follicle stimulating hormone. And there are no follicles in the testes. So it's really a misnomer. It's a feminine name but we're stuck with it anyway. The target of FSH in men are the seminiferous tubules which produce sperm through the process of miosis as we said. Then there's ICSH which stimulates the interstitial cells. Those produce testosterone which we said makes the production of sperm possible. In other words, could you have fertility with FSH alone? No. Because you would lack what? Testosterone. No testosterone, sperm production would falter. So both these hormones are necessary and both are absent in boys, thankfully. And so naturally this happens, the arrival of these gonadotropins occurs with puberty. Of course this begs the question, why does the anterior pituitary suddenly wake up one morning and start to crank out these hormones? Actually it's not the pituitary's decision. What makes this decision for the pituitary is actually the hypothalamus. The hypothalamus releases GNRH, which stands for gonadotropin releasing hormone. And once that is released, then the anterior pituitary begins to crank out FSH and ICSH. The former targets the seminiferous tubules and makes sperm. The latter stimulate the interstitial cells and make possible the release of testosterone. We show an arrow from testosterone over to sperm which reminds us that sperm production is dependent on what?

>> Testosterone.

>> Steve Langjahr: Now is testosterone confined to the testes? Well, of course not. It's a hormone. Does it get out into the blood and have effects elsewhere? Naturally. And among its effects elsewhere, it actually feeds back and has an effect on the pituitary and/or the hypothalamus. So whenever there's high levels of testosterone, what will that do to the release of FSH or ICSH? Inhibit it. What's the name of this process where high levels of a hormone shut down the release of these gonadotropins?

>> Feedback.

>> Steve Langjahr: Negative feedback. So a man that's taking testosterone for the sake of bodybuilding, injecting himself with testosterone, will he big and buff and strong and impressive and get a lot of dates? Yes. But what's happening to his anterior pituitary, and for that matter his hypothalamus as a result of this testosterone intake? That's going to be shut down. What then would happen to his sperm count you think? Sperm count goes down. Which might be perfectly fine with that individual, if they're not interested in becoming a father. So it's a kind of birth control. Now the question that's unanswered here is how does the hypothalamus know to release GNRH? That question is kind of murky. Once again, because the hypothalamus is the brain. But we know that it's sensitive to a hormone actually produced by another part of the brain, the pineal. The pineal body or the pineal gland. The name of that hormone is melatonin. From

anatomy, you recall that melatonin inhibits these, that is inhibits the release of these two gonadotropins. And therefore is responsible for suppressing puberty, that is preventing or at least determining the onset of puberty in both sexes. Now another interesting and more or less recently discovered hormone which has an effect here is actually strangely a compound produced by adipose. And it's given the name leptin. Leptin what? Leptin released from fat increases the release of what? G – here it is. GNRH. And if we boost more of this, we're going to have more stimulation to the anterior pituitary. We'll stop with this remark, but here's an interesting way to at least appreciate the role of leptin. Leptin comes from what? Adipose. Now switching our attention to females, what's been your observation? What have you read or what do you know about the onset of puberty in girls? Is it happening later in life or earlier in life? Earlier in life. Back in the 1960's, menarche was age 13 or 14. Now it's age 9 or 10, believe it or not. And so people are starting to get panicky. They think something must be in the food. Something must be in the water supply. But it's probably not that complicated. Because what do we know about people in the US of A in general? They're fat. And there's no way to sugarcoat that. One-third of the population in the US of A is the O word. What?

>> Overweight.

>> Steve Langjahr: And is this happening in young children?

>> Yes.

>> Steve Langjahr: Yes. Why? Because we drive thru, drive thru, drive thru. You get my point. So are females endowed with more adipose? Yes. Therefore they have more what? Leptin. What does this do? Triggers the release of GNRH. So the onset of puberty might be tied with adiposity. And even though that seems odd, think about it. Why would there be a link between body weight and reproductive readiness? Reproductive readiness. Is there some connection between the amount of adipose you have and your suitability and readiness for parenthood? As a woman especially, what does it take to get pregnant and stay pregnant? Energy. In the form of what? Adipose. So if you have a lot of adipose, that's telling your body, "We're ready to get what? We're ready to get pregnant." Of course that's sadly not the case. But it does explain the connection with adipose. We'll overlap and come back to this on Wednesday and of course move on to the female at the same time. If you didn't get the weekly sample exam last week, there are supplies over there. And the answers actually went up and are up on the webpage.