>> Steve Langjahr: It's November 22nd, the day before Thanksgiving. Lecture 27. Our first look at this endocrine system that's familiar from anatomy. We should start naturally with the definition, what is an endocrine gland? By definition, this is a gland which has no ducts to the outside, rather it secretes to the circulatory system. And so these endocrine glands communicate with each other and with so-called target tissues through chemical messages which of course are called hormones. A hormone by definition is any compound, any endocrine secretion which is transported by the circulatory system and it has an effect or effects on one or more so-called target organs. What that means is an organ is sensitive to a hormone and reacts accordingly. Before we get down to what you'd expect, you know, kind of a survey of all the endocrine glands, let's talk generally about how hormones work. And to do that, we have to begin with this description and that is hormones come in one of two basic varieties, those that are water-soluble and those that are fat soluble. So with that in mind, their mechanism of action differs. For those hormones that are water-soluble, they really do not and need not actually enter the target cell. Instead, these hormones attach to receptors on the cell membrane, receptors dedicated to that particular hormone. And the attachment of that hormone then causes some internal activity, which includes activating an enzyme called adenylate cyclase which converts existing ATP into a compound called cyclic AMP. What do you think M stands for? If T stands for tri then M stands for mono. I have the formula for cyclic AMP up here, not that you need to copy it, but it's called cyclic AMP because the single phosphate forms a kind of ring at the end of the adenosine. I just wanted to give you some justification for the name, not that it matters a whole lot for us. What does matter is that cyclic AMP is ultimately the trigger which causes some change in the activity of this target organ. So, sort of unexpected, the hormone itself doesn't trigger the response. The hormone is actually designated the first messenger. Cyclic AMP is the second messenger which then causes a change of activity within the actual target itself. So, in short, it's kind of an indirect or one step removed sort of mechanism. And this applies again to water-soluble hormones. Essentially, the hormone does not and need not actually enter the cell. It attaches to external receptors and brings about some response which is very often a change in enzyme activity, a change in membrane transport, or maybe even a change in the degree or kind of protein synthesis that's going on. Water-soluble hormones as a matter of fact tend to be proteins, peptides or amines. All of these are nitrogen-based compounds which are water-soluble. And from time to time we'll of course emphasize or at least make reference to whether a hormone is a peptide and amine a protein or something else. But remember there are two kinds of hormones, those that are water-soluble and those that are fat soluble. Now fat soluble hormones have a whole different strategy because after all what's the cell membrane made of but phospholipid. So, a fat soluble hormone has no trouble wandering in, that means getting inside the target cell or any cell for that matter. And so the receptor for fat soluble hormones is not found on the cell membrane, but actually found inside the cell, very often in the nucleus. So this is a whole different approach. In other words, fat soluble

hormones act on intracellular receptor sites, not membrane receptor sites. And, of course, when we talk about fat soluble, we mean mainly steroids and there are many hormones that we'll mention and already have mentioned, which fit this description, that is they're fat soluble steroid hormones. So, their action is basically to alter enzyme or protein synthesis but they do so inside the nucleus attaching to receptor sites there. So, we don't want to make a huge deal of this except to make you aware of the fact that there are two kinds of hormones, those that are water soluble, those that are fat soluble, and they work by these very different means. As a matter of fact, then the intracellular receptor sites which are triggered by fat-soluble hormones tend to require a little more time. And so, what I've just tried to say is water-soluble hormones tend to work quicker than fat-soluble hormones, just as a general statement. So those are then the general mechanisms of hormone action. Let's go to this category before we get specific. And at least list some of the factors, some of the ways in which hormones can be regulated, in other words, ways in which endocrine glands can be controlled. It turns out that some endocrine glands are under the thumb of the ANS. What's that? Autonomic nervous system. Now, of course, not all endocrine glands are even connected to the autonomic nervous system, but at least some would fit this description. An example would be the adrenal medulla. And as you know, the adrenal medulla produces epinephrine and norepinephrine which are, as you know, directly released as a result of increased sympathetic activity. So this one example shows the connectivity between the endocrine system and the nervous system, certainly wouldn't want to leave you with the impression that the endocrine system is somehow independent or self-sufficient. In this case we see a direct connection with the autonomic nervous system. Here's a surprise, item B, some endocrine glands are controlled by other endocrine glands. Maybe it's not a surprise but it is true and there are many examples in this category. As we'll see later today the pituitary is a prime case, because it's controlled by so-called releasing hormones, which are actually manufactured and set loose by the hypothalamus. I suppose you could argue that this is a case of an endocrine gland being controlled by the brain. But because the hypothalamus is producing actual hormones, essentially it's hormones controlling hormones. So, this is just another kind of control mechanism. Some endocrine glands are completely independent from A and B. Some are entirely sensitive to, responsive to the presence of organic compounds in the bloodstream. A good example here would be of course the pancreas. What two hormones did we mention on Monday coming from the pancreas are sensitive to something in the blood? Yeah, insulin and glucagon. And what is that something that they are sensitive to? Glucose. So that's a prime example of an endocrine gland being controlled by some blood concentration of an organic compound. Some endocrine glands are controlled by changing levels of inorganic ions. And a couple that come to mind here, the parathyroid which we've yet to mention is very sensitive to and controlled by changing levels of calcium. And there's even another one, aldosterone. What inorganic ion is indirectly involved in triggering the release of aldosterone? Sodium. So, we don't have to really go on and on, we're just trying to give you examples that fit each of these control

mechanisms. Now, aside from A, B, C and D, pretty much any endocrine gland is also, to some degree, controlled by something called a feedback loop, which you may have learned about in biology and here we go. A feedback loop is basically a situation where the output, that means the hormone produced by endocrine gland, actually affects the input, usually stimulates the controlling gland. Now, that sentence probably as pretty, pretty unclear and I think you can really distill what we're about to say in a very familiar remark. And you know how it goes. What goes around comes around. And do hormones go around, and do they come around? So, although that's just an analogy, it's the essence of a feedback loop. In fact, after all, what's a loop really mean? A loop is a circle. And that means there's some connectivity at the start and at the end. So, let's get real, let's give you an example or at least a diagram. Let's talk about the pituitary gonadal hormones which fit this description particularly well. And let's start with a controlling gland. A controlling gland, just call it gland A, and that puts out hormone A which then has a positive effect on gland B. So far so good? The controlling gland puts out a hormone which stimulates yet another endocrine gland. And endocrine gland B produces a hormone. Let's call it hormone B, which has this effect or that affect on a given target organ. OK. But does this hormone produced by gland B, does it circulate and reach back and have an effect on the controlling gland? Yeah. And so, levels of this hormone have a profound effect on the controlling gland. And notice the symbols here, that effect can either be positive or negative and therefore crank up or crank down the release of this controlling hormone, hormone A. So, this is the essence of a feedback loop because it is indeed a circle. And in so many words, the output, the output from a gland affects the stimulating gland in ways that we're about to describe because there are actually two kinds of feedback and when we're done, you could argue there's even three. But first, negative feedback. That term is almost in your day to day vocabulary, isn't it? You say, I got some negative feedback on that, meaning you heard something that made you reconsider something. But in this context, negative feedback is as follows. It's wherever we have a high level of a given hormone, which indirectly inhibits its further secretion. So, let's walk through this using the diagram. Gland A puts out what? Hormone A, which stimulates gland B, which then releases hormone B. And when hormone B increases, when high levels of hormone B occur, when high levels of a hormone occur, they may have what effect here? And what do you call that when they inhibit the controlling gland? Negative feedback. Now, it's easy enough to accept that, it's more important to understand why it's important. And it's really pretty simple. Think about it almost logically, does it make any sense to crank out more of this hormone if you already have plenty of it? And wouldn't it be prudent to somehow decrease its production, and that in fact is the purpose of negative feedback, to control, to keep in check the overproduction of a given hormone. It regulates and prevents the oversecretion of a given hormone. What's it called? Negative feedback. And it's almost self-explanatory once you sort of appreciate what we just said. Now, negative feedback also can be removed and it works just like this. If something inhibits the production of that hormone, then it obviously won't be exerting any

more what? It won't be exerting negative feedback. And it would be tempting to call that positive feedback but it's not. It's just the removal of what? It's the removal of negative feedback. It's kind of like what you do in your car. You have your foot on the break. That would be like what? And when you take your foot off the break, that's not positive feedback, that's the removal of negative feedback. So, negative feedback occurs when there's high levels of a hormone. The removal of negative feedback occurs when there's low levels of a hormone. So, to be clear, this is negative feedback. You can either have it or you can take it away. Neither of those is positive feedback. Before we go to that, you can probably already predict what positive feedback would be even thought it might seem– even though it should seem rather inappropriate. Positive feedback, believe it or not, is when high levels of a given hormone, when high levels of a given hormone actually what? Actually stimulate that gland. And if you think about that, that's going to only crank out what? More, which then would stimulate what? More. Which would stimulate more, which would stimulate more. And the reason that's so illogical is that, obviously, there would seem to be no end to that. More would get more, which would get more, which would get more. And for that reason, positive feedback is not very common because it leads to an out of control situation, which is usually interrupted or halted by some event. So, even though positive feedback sounds illogical, as we'll see later today, it's actually beneficial because it escalates, you know what that means, it accelerates something. It makes something happens sooner and therefore as we'll see, can be beneficial especially in this case of pituitary and gonadotropin hormones. So, as we leave this page, we've talked about feedback. How many kinds are there? Two. Negative feedback is when we indirectly inhibit the further secretion and positive feedback is when we indirectly accelerate and stimulate more of the secretion. So, negative feedback can be applied or removed and positive feedback is a rather rare case where you actually accelerate and bring things into play quite a bit quicker. We'll have examples of all of these before long. So now, with all of that background, we should and could start talking about hormones, specific ones. And if there is a kind of master gland in the endocrine system, you probably know from anatomy that the pituitary fits the bill. The word pituitary is kind of a– well, it's a misnomer because if you look at the etymology of the word, pituitary means mucus. So it was a bad name from the beginning. And so the more modern name for the pituitary is the hypophysis. Which as you may know from anatomy is not even a singular structure, although you know it resides in that little pocket, that little saddle of the sphenoid bone called the sella turcica. So, it turns out, the pituitary, which is no bigger than a green pea, is actually two glands, quite independent and quite different. The first part, the larger part, the anterior part is just called the anterior lobe. Its formal name is adenohypophysis. The prefix adeno means gland, an actual epithelial structure. And so we say it's made of glandular epithelium. Now the back part, which is smaller, you can see here in yellow, is actually literally physically connected to the hypothalamus. And so you're not surprised to find that it's made of nerve tissue. It's called the neurohypophysis accordingly and you could argue that

it's really just a part of the brain, specifically the hypothalamus. So, these are anatomical distinctions. I'm just trying to refresh your memory and make these terms familiar again. So, naturally, what we should do, what we need to do, is jump in and start naming of the endocrine hormones that are produced at these two locations. And not just name them but give them some function and even some reference to how they are controlled. So, let's start a list, the anterior pituitary hormones. First one is somewhat self-explanatory. It's called TSH. That's an acronym for thyroid stimulating hormone. Let's all guess what that does. Yeah, it stimulates the thyroid gland. Two. Next one is called adeno– adreno, I should say, corticotropic hormone, that's a mouthful. But it's really just a conglomeration of words. Tropic means to stimulate. So, apparently, this is a hormone which stimulates the adrenal cortex. So, it really couldn't be a better name. If you don't like saying that, just call it ACTH as long as you know that stands for adrenocorticotropic hormone. And obviously, what it does, it stimulates the adrenal cortex. The meaning of that will become clear when we learn more about the adrenal cortex, for now, that's all we need to say. The third one is deceptively simple sounding. It's called growth hormone. And you'd be quite right to assume that it stimulates growth but that doesn't imply that it's only useful in childhood. It's important throughout life as we'll see. Its acronym is hGH with stands for human growth hormone, which of course is very species specific. And we'll get to its actions which incidentally are far beyond just growth. In fact ever– if there ever was a hormone which was oversimplified in terms of its name, it's growth hormone because it does way more than contribute to growth. In the opposite way, prolactin couldn't be much easier. Prolactin, abbreviated PRL, is a self-explanatory name if you really tease apart the elements. Pro doesn't mean professional here, unless you're a professional lactator. And I guess there are people that make money lactating. That was a lame attempted joke. OK. But pro means to promote. To promote what? Lactin, lactate, lactation, the production of milk. And right away you'd probably dismiss that as not so important. Certainly not so important if you're a male, although you should be thankful for that even as a male. But certainly it's important in women as a result of delivery because it provides a resource for milk production as you'd guess. Now the next couple of hormones, again, we're still talking about hormones produced by the anterior pituitary. These are listed here as gonadotropins which is a category, a subcategory, and the name is self-explanatory. Tropin means to stimulate. So apparently, let's guess, these must stimulate what? Gonads. If you're a male, your gonads are your testes. If you're female, your gonads are your ovaries. And maybe surprisingly, the hormones we're about to name are chemically identical in both genders. They're chemically the same but obviously, they target different gonads in each of the two sexes. So, what are they? We said there are two. The first one is named for its feminine effect and it's called FSH, follicle stimulating hormone. It's pretty obvious from the name that it's a hormone that stimulates follicles, but that's maybe not that specific. Follicles are units, structures inside the female ovary which ultimately blossom or produce on a monthly basis a single gamete, namely an ova. And obviously you would assume that FSH is present

only as a result of puberty. In other words, do we have five year olds of either sex with FSH? Thankfully not. And the second one, the sixth one here I should say, is LH, luteinizing hormone. That's the name that's used for females. In men it's called ICSH, an acronym for interstitial cell stimulating hormone. Perhaps you recall these from anatomy, perhaps not. But both of these are– both of these are what? Gonadotropins. Both of them are necessary for fertility, both of them are absent in juvenile years, and both of them of course make possible sexual reproduction. So, as we look back on this list, we have a bunch of asterisks here, asterisks, asterisks, asterisks, and all of those are, as you can see, tropic hormones, which means they basically control the secretion of other hormones and these will crystallize or become clear later as you learn more and we get further into these. You see, what we've done here is just name them. We really haven't gotten into their actual actions or importance, although some of these are important just at a glance. That is we can tell or predict their importance. But we're going to give you a lot more information. Now, without getting specific to any of these six, can we say something about the control which is exerted on the anterior pituitary and therefore to some degree on any or all of these individual examples. And the answer is yes. And so, in general, these hormones that we've named are controlled by negative feedback to some degree. So, let's take a case in point. Here's a hormone we just named ACTH. That comes from the anterior pituitary. And the name tells you that it stimulates the adrenal cortex. Among the hormones that are released from the adrenal cortex is this one you may or may not know is called cortisol. And it has various effects on various targets. But remember, what's the essence of negative feedback? Whenever there's high levels of these or similar hormones, does this hormone get back to or have an effect on the original controlling gland? The answer is yes. And so, to make the case, high levels of cortisol have what effect on the anterior pituitary? Negative. And to remind you, why is that good, why are we happy that high levels of cortisol will shut down or at least inhibit the release of ACTH from the anterior pituitary? Why is that good? Well, we've got high levels of this already. Do we need to make more? Probably not. So, again, this keeps things in check and therefore prevents the needless overproduction and perhaps actually damaging effects of too much hormone. And just to remember, what would you call it when there's low levels of cortisol? Low levels of cortisol would remove what? Would remove negative feedback and therefore instigate the release of ACTH which then would restore or return cortisol levels to a normal value. So, between, negative feedback and the removal of negative feedback, a given level of a given hormone is kind of guaranteed or assured. But before we go on, it's pretty clear that negative feedback doesn't cause this to happen, it just more or less controls it once it's underway. So the real question that emerges from this, OK, I get that but what cause the anterior pituitary to release this in the first place? In other words, we understand this feedback thing but what cause the anterior pituitary to release ACTH at all? There must be something else that triggered or began this whole process. And that something else is a whole slew of hormones that trickle down from the hypothalamus and these then are called RH or releasing hormones. So what we've just answered was

that question. What controls the anterior pituitary? H word, hypothalamus. And specifically, what are these releasing hormones? This gets very wordy so I apologize but that's science. The first one is what? TRH, which you can guess is called thyroid releasing hormone. Now, let's not misunderstand that. What is it called? Thyroid releasing hormone. That doesn't even touch the thyroid. Thyroid releasing hormone stimulates the anterior pituitary to release TSH and therefore gets the ball rolling toward the ultimate stimulation of the thyroid. Well, that's good, let's move on. Then there's CRH which stands for cortical releasing hormone. These two doesn't touch the adrenal cortex, it stimulates the anterior pituitary to release ACTH and on and on. Then I told you this is going to get busy. The next one is GH-RH, whoa, growth hormone releasing hormone. Could these get any more wordy? And as if that weren't bad enough, we have GIH which stands for growth inhibiting hormone, also known by this alternative name, somatostatin. But it is what it says, it stimulate– I should say it inhibits of the release of human growth hormone. Then this one, which is going to be very important, GnRh, which stands for gonadotropin releasing hormone, which therefore I– or therefore causes the release of FSH and ICSH. So– well, there's one more, PIH, which is what? Prolactin inhibiting hormones. There are even others but these are the important releasing hormones. And why as a general statement are these important? All of these answer the question. What was the question? Here's the anterior pituitary, it releases this, but what causes the anterior pituitary to begin those or release those in the first place? It's basically the hypothalamus, which begs another question then. Because the answer we just gave makes us wonder about the next question. If we've just said that the anterior pituitary is controlled by the hypothalamus, what's the next question? What controls the hypothalamus? Now that's when things get very, very murky because what you're really asking there is what controls the brain. And that might not even sound like a question, I mean, what controls the brain? Well, the brain. So that's a difficult thing to answer and in fact we can't except that we can at least add and say again that the hypothalamus, which controls the pituitary and the ways we've just mentioned is also subject to feedback. So we see this feedback story can be expanded or pushed back a little. You see here's where we were before. We started with the anterior pituitary. We said it released ACTH. We said that stimulated the adrenal cortex. We said that released cortisol. We said that had what effect here? Negative. Now, we're saying in addition, this hormone not only inhibits the anterior pituitary but it also inhibits the hypothalamus, therefore reducing its own release of CRH. So, I know this is confusing but it's the way it is. It's a loop. It's actually two loops. This is called the short loop, this is called the large loop, but all of it adds up to negative feedback. But even though this seems like we're asking and answering a question, we're not. What do I mean? We ask the question, what controls the anterior pituitary? We said the hypothalamus. Then we asked the question, what controls the hypothalamus and we said negative feedback. But negative feedback keeps things in check but it doesn't necessarily explain how and when and why the hypothalamus release this hormone in the first place. So, clearly we get into murky territory. Because remember, the hypothalamus

is part of the brain. And so we're asking the question, what controls the brain? Well, everything does. Now I know that's kind of an escape clause there but all we can say without getting bogged down is that neural input from other areas of the brain very definitely, in ways that we probably don't even fully understand, control the hypothalamus. And is the brain controlled by outside influences? Is the activity of the brain subject to influences, environmental, I mean– Well, what do we have here? Environmental factors like what? Stress and light. Is your body, in ways that you probably even know, influenced by light? There's something, you know, the daily circadian rhythms, light, dark, light, dark and we might dismiss that as just sunrise, sunset, but light is definitely a cue, a trigger, a control mechanism working through and on the brain, into the hypothalamus. And who doesn't accept the fact that stress affects the brain? And by stress we mean emotional stress or physical stress, infection, conflict and so forth, and therefore can stress influence the endocrine system? I know these are kind of general remarks but can stress affect the brain and can the brain affect the hypothalamus and can that affect the endocrine system? Can reproductive cycles, can hormone secretion be influenced, upset, altered by what? Altered by stress and light. The answer simply obviously, yes, in ways that we probably don't fully understand but all we can say is definitely areas from within the brain and environmental factors do affect the release of hormones. So, let's press on. We've just sort of scratched the surface on the anterior pituitary. Let's spend a moment on the posterior pituitary, which I'll tell you upfront is a lot easier, in other words, a lot less going on here. The posterior pituitary produces actually nothing, and that sounds preposterous. There are two hormones that come from here but they're actually produced by the hypothalamus. That's a technical fact. And the two hormones that are restored and released from the posterior pituitary are probably familiar. First one is OT which is an acronym for oxytocin. It's a peptide. So, incidentally, is it water soluble? Yes. And the other hormone, one we already know about, quite a bit about, and that's ADH, also called vasopressin. ADH is an acronym, you know, for antidiuretic hormone. It's a peptide, it's a water-soluble hormone, and you know its primary target is the nephron specifically the collecting ducts. So you know way more about ADH than you do oxytocin, at least in this moment, but let's go on. What are the actions of these two? The one that you've just heard or maybe recall from anatomy, OT, what's that stand for? Oxytocin. In clinical, in hospital settings, this is called Pitocin but it's named for its effect and its primary effect is directed on reproductive smooth muscle. Now, in women, what is the largest concentration of smooth muscle in the reproductive system?

>> Uterus?

>> Steve Langjahr: Uterus. So, in simple terms, its main target is the uterus. And it stimulates the contraction of the uterus and therefore would be useful and expected in what scenario or what period of time? Childbirth. And if you know from clinical work or what have you, Pitocin is given to women to either induce labor or cause contraction of the uterus after delivery. So it has that very familiar clinical advantage. But of course, you wondered, do men have oxytocin,

and if so, what's it doing? Well, in men, it stimulates the prostate, especially as result of sexual activity and causes or improves the release of semen. So, its role in men is kind of subservient and less than impressive. Certainly, in females, it's very important for delivery, labor and delivery. Now, what about ADH? Well, we know a lot about that, we just said that's its action is on the nephron. And here's the bottom line which the acronym itself says. I mean, let's remember, antidiuretic. What does that even mean? Antidiuretic, it stops or reduces urine output. So, that's exactly what it does. It promotes water reabsorption, therefore minimizes water loss. It's a great name. Now, with those actions on the table, what are the ways that these are controlled? Right up front, you would assume and you'd be right that these are controlled by totally different things. In other words, the things that control ADH should not and would not have any effect on oxytocin. These are very different hormones with very different intentions, very different functions. So, when we speak of control, it will be very different for these two. However, they are both controlled by APs. What's that? Action potentials from the hypothalamus. There is no releasing hormone. So, this is a neurological, a neurological release of these hormones in response to various things. And what are those things? For OT, the primary trigger is suckling. That means an infant nursing at a mother's breast and/or what? Uterine stretch. Now, when does the uterus get stretched? When is its maximum stretch achieved? Just before delivery, right? So, this is almost too logical. What would you hope uterine stretch would do with respect to the release of this hormone? I mean, after all, this hormone stimulates the contraction of the uterus. So would you expect a tight correlation there again? So, here's the story without being oversimplified. Baby gets big, baby stretches the what? Uterus causes the hypothalamus to create what? APs, which cause the release of oxytocin, OK? Story is not ended. Oxytocin causes the uterus to what?

>> Contract.

>> Steve Langjahr: Contract. And that puts the baby's head into the cervix, which causes more, S word? Stretch. And more stretch causes more what? And more oxytocin causes the baby's head to move further into the cervix causing more what? Stretch, which causes more oxytocin. What's this sounding like? Positive feedback. In other words, stretch, more oxytocin. Oxytocin, more contraction, more stretch, more oxytocin, more oxytocin, and that's OK. In fact, it's not only OK, it's welcome. Why do we want to move this along? Do you want to be in labor for a couple of weeks? I don't think so. It's not just bad for you, the mom, it's not that great for the infant. So, accelerating and bringing about a rapid conclusion to this is the beauty of positive feedback. Now, what about this, suckling? This has nothing to do with delivery or labor. But suckling has to do with lactation and the letdown of milk. So, if an infant is sucking on a nipple, will that promote the release of this hormone and will that hormone promote more release of milk? And what would more milk probably result in from the behavior of the infant? If the infant gets more milk, then that's sort of a positive cue that this is working and I better suck more, right?

More sucking, more oxytocin, more milk and just, you know, a cascade of milk. What breaks that cycle is usually the mom. She just says, well, I've had enough of this, or passes it on to the dad and he doesn't know what to do. But anyway, positive feedback can apply to milk letdown and also delivery of an infant, the classic case, a beautiful case of positive feedback. Now ADH, of course, a whole different story. You know and certainly will integrate these ideas as you prepare your report. ADH responds to extracellular osmolarity and also blood pressure changes. Remember the osmoreceptors and the pressoreceptors, all of those mechanisms, which obviously determine how much and when ADH would be secreted. So, those are the two hormones produced by the hypothalamus only stored where? They're stored and released from the posterior pituitary. And we will revisit them a bit. But let's move on to Roman numeral V, the thyroid gland, which is a complete, out of a box story, meaning the thyroid has little to do with anything we said so far. It is controlled by the pituitary. And let's start with a statement, a necessary reminder of the hormones that are produced here. And there are two, one perhaps more familiar than the other. Number one, TH, which is an acronym for thyroid hormones. Notice the plural, because there are a number of thyroid hormones that are chemically very similar, that is their amines. An amine is a nitrite– a short, very small nitrogen base compound, a water-soluble hormone. Now, the thyroid hormones are manufactured, of course, in the thyroid gland. And in case you forgot, the thyroid gland is in the neck, right below the thyroid cartilage. It's the largest endocrine gland, not that we'll ever ask you that. But what goes on here is there is a glycoprotein called thyroglobulin, which is manufactured here. And the cells of the thyroid very aggressively remove I2. What's I2? I2 is elemental iodine from the blood. In fact, this is the one and only case of active transport for iodine, which means in so many words, 99% of the iodine in your diet ends up where? Ninety-nine percent of the iodine in your diet ends in the thyroid gland through very aggressive active transport. And why should that be? Well, one of the rather rare purposes of iodine is to create these two hormones because the thyroid hormones contain and require elemental iodine. OK. So, what? The addition of iodine to this glycoprotein produces what's called iodinated thyroglobulin, which is stored inside the thyroid follicles. In other words, it sits there waiting for some signal. And incidentally, what would that signal be? You already know. I mean, what's the name of the tropic hormone that pours out of the pituitary which causes the release, you think, of this hormone? TSH, thyroid stimulating hormone. Now, we haven't told you what causes TSH to be released. We'll do that in a minute. But at least you know that this hormone is going to sit there until the signal in the form of TSH arrives. And when that is– or a signal of the iodinated thyroglobulin is released into the bloodstream in one of two forms, it's released as T3 or T4, and those designations are not arbitrary. Notice T3 is the name, the shorthand for triiodothyronine, whereas T4 is tetraiodothyronine. And that shouldn't be hard. Which of these has three iodines, which of them has four? You can figure it out. Now, without getting too super technical, both of these are TH. They're both what? Thyroid hormones. The most important of the two is T4, which also goes by the name of thyroxine. OK, so what? Well,

let's suspend that story for the moment and cover the second hormone also produced here, which surprisingly has nothing to do with thyroxine, proving that this gland, the thyroid gland, is not a simple, you know, one-trick pony here. It actually produces a very different hormone called calcitonin, which is a larger water-soluble peptide. So, with those statements on the screen, let's revisit them now and give purpose or function or action to these. The most important, far and away, of these two hormones is T3 and T4, aka thyroxine. And their effects are widespread and significant. Widespread meaning that these hormones don't have a specific discreet target. T3 and T4 probably affect all cells of the body. In other words, there's no specific but rather a generic influence on just about every cell in the body. And read on, what do these hormones do? They promote the synthesis of mitochondrial enzymes, which of course mean Krebs cycle enzymes which means enzymes fostering the citric acid cycle and thereby feeding the electron transport chain. In short, in a simple statement, these hormones stimulate metabolism. They stimulate ATP production by virtue of increasing the synthesis of these enzymes. And therefore there are net effects. Their bottom line effect is that they promote an increase in BMR, an acronym we defined already. What's BMR? Basal metabolic rate. And one of the obvious offshoots of that is not only producing more ATP but also consuming, consuming more oxygen, and as byproduct producing H-E-A-T. So, if you want a simple statement, these hormones, the thyroid hormones, accelerate metabolism, accelerate the consumption of oxygen and also the production of heat. So they positively boost metabolism. And incidentally, and not unimportantly, T3 and T4 work synergistically with HGH and insulin to promote, what you said, protein synthesis and accordingly growth. Now when we think about growth, we can and should think about growth through childhood. And what is growth? It's not just gaining weight. Growth is mitosis. And what is necessary for mitosis is protein synthesis. So you start to see a connectivity here. And what we're saying, growth is not just a function of HGH, what's HGH, human growth hormone. It's also a cooperative effort between at least these three hormones. What three hormones are involved in ordinary growth? HGH, insulin, and now we're saying what? T3 and T4. This is very important, especially and obviously in infancy to the newborn. In fact, it's a state law at least in California that newborns be checked for their levels of T3 and T4. That's done right on day one or may be day two of it's a weekend. So, why is this important? Well, if these T3 and T4 levels are low, then obviously that's going to inhibit what? And by growth, we don't just mean getting bigger, growth affects every tissue including and mostly the brain. So the reason this became a law is that this is easy to fix. What do I mean? If an infant has a low thyroxine, is that easy to fix? Is it worth fixing? And do you get a second change? Can you say at age five, oh, we missed that? No, done deal. So, it's very important to get early handle on this. And so T3 and T4 are naturally and importantly measured in newborns, because if they're low, they can be replaced. And this provides an opportunity to mention HRT. This is an acronym. We'll mention it more than once. HRT, hormone replacement therapy. And that is the universal and simplistic remedy for any deficiency of any what? If any hormone is low, the obvious thing to

do is to give that hormone and that, in any other name, is called HRT. So, OK. Now, what about calcitonin? Calcitonin, we didn't give you any information, but it's somewhat self-explanatory. It would seem to have something to do with calcium. And actually CT is an important agent which responds to what? Low levels of what? Well actually, I'm sorry, I get this backwards. It actually lowers calcium and therefore promotes the removal of calcium into bone. So let's restate that. It takes calcium from where? From the blood. And puts it where? So, a simple assumption, a correct assumption, is that it helps strengthen bones. Hence the name what? Calcitonin. So that's its effect, which I implied correctly is certainly stimulated by or triggered by calcium levels in the blood. And so as we move into this, we've already sort of given you hints about how these two hormones are controlled but not so much with TSH or TS– or TH. Thyroid hormones, we just said a moment ago, are obviously controlled by TSH, but that doesn't really complete or satisfy that question, because TSH comes from the hypothalamus. And what did we say a while ago? The hypothalamus is the brain. The brain is controlled by, well, itself and all sorts of what? All sorts of environmental factors. And it turns out that this is a classic and pretty well-established connection, because the environmental factor here is environmental temperature, climate, climate. And that might seem odd or surprising, but basically this hormone is released by TSH in response to changing environmental temperatures or changes to internal BMR. Specifically, it's this, when there's high temperature in the body or in the environment, that actually inhibits TSH. And when there's low temperature in the body or in the environment, that actually stimulates the release of TSH and therefore thyroid hormones. Now, that might went by pretty fast and it might not have even made any sense. But let's retrace that. If there is low environmental temperature, what release more or less of this hormone would be helpful? Remember, one of the byproducts of this hormone is what? Heat production. So, if you're in a warm environment, do you need to generate heat? No. When you're in a cold environment, would heat be helpful? Would it be sustaining? And so, now it makes some sense. Essentially, this hormone bolsters metabolism, therefore warming the body very literally through the offshoot of heat. And so, environmental temp or body temp or even changes in natural BMR can upset or I should say turn up or turn down the release of this hormone. Now, calcitonin, totally different, we implied a moment ago that basically it's sensitive to blood calcium, specifically it responds to high calcium and therefore, does what? When the level of calcium is high in the blood, where hormones released, what does it do? It lowers it. Where does that calcium go? In the bone, thereby strengthening bone. And so naturally, that makes some sense. When it comes to these endocrine glands that we're about to move further into, we'll always devote a section to this and that's disorders. And so with an introduction to that topic, an endocrine gland either can be working fine, OK, or can be what? Working fine, underproducing or what? Overproducing. Those are the three possibilities. And when it comes to disorders, we don't care about normal, we care about over or underproduction. So naturally, we have to think about what would be the impact of too much TSH or not enough TSH. And the names for

these syndromes will always be prefaced by a prefix hypo or hyper. Now, what do you think hypo means, hyper? So you got it. So hypothyroidism is just what it sounds like, underactive thyroid gland. And incident– incidentally, rarely is calcitonin part of the conversation. In other words, these cells hardly ever fail. So when we talk about hypothyroidism, we mean low levels of T3 and T4. And you can predict. You should be able to predict. Don't memorize. Predict what would be the effect. If we don't have these hormones, then we're not going to be synthesizing mitochondrial enzymes, therefore we're not going to be bolstering BMR. We're not going to be increasing heat production, essentially we're going to tune down metabolism. So, when there's hypothyroidism, it goes by the name myxedema, which is a strange name. We can learn more about it in your text. But the bottom line in terms of symptoms are these. Low BMR, what's that? Basel metabolic rate. Lethargy which means being lazy, sitting on your butt. And when you have no energy, no pep, and you continue eat, guess what happens. Let see, no pep, sitting on butt, and you're still eating, that's going to be what? So, let's make it clear. Weight gain is an indirect and not always obligatory effect, but it sometimes occurs as a result of lethargy. Still, other symptoms are equally important, not the least of which is this one, intolerance to what? Cold. In fact that's usually the statement that gets the attention of some practitioner, meaning a doctor, nurse, whatever. So a patient says, I don't know what's wrong, doc, but I just I'm cold all the time. So unless the person missed that day in physiology, they say, "Oh well, probably we should check your thyroid. Now the other affect which is harder to explain at least in simple terms, is that in adults, this causes a lot of subcutaneous fat and other material under the skin, so it causes some very characteristic, very striking facial feature changes, which are recognizable although not particularly troubling. Again, the troubling thing is that these people say what? I just am what? Cold all the time. Now, before going on, is this an easy fix? In other words, can we treat– not cure but we can we treat hypothyroidism? Yeah. You just give him what? And you probably know somebody who's on thyroid, which means they're taking daily tablets of thyroid. Because presumably they're what? They're hypothyroid. Now, much more important or dangerous is when this happens in newborns and we implied that this is serious because it controls and determines growth. And in fact, this is a horrible thing called cretinism, which leads to not just physical reduction in growth but mental and physical retardation. A cretin is a sad tragic case where the nervous system doesn't develop and therefore you have permanent irreversible mental retardation, hence the importance of measuring this hormone. What's the flip side? The flip side if we're talking about thyroid is not under but overproduction. And this is called? Hyperthyroidism. It also sometimes called Graves' disease, which is an eponym named after a person. Guess what's his name was? There you go. And not surprisingly this has the opposite effects. Instead of low BMR, we have high BMR. What's HR?

>> Heart rate.

>> Steve Langjahr: Heart rate. What's this? Nervousness. Sometimes this is part of a complaint that means the patient will come in and say, I don't

know, but I'm just hot all the time. And at the same time they're tapping their toes and they're not sitting still. So, that's usually a clue, again, unless that person missed that day in med school, that probably this is what, hyperthyroid. There are maybe weight loss, but I want to make it clear because too often this is oversimplified. People say, oh, you're skinny, you must be must be hyperthyroid. Oh, you're overweight, you must be hypothyroid. Well, that's not even true. There maybe rather lose correlation here. But weight gain or weight loss is not unfortunately, due to a single hormone, certainly not thyroid. Here's an interest– You don't have these but this is another change. We mentioned facial changes, myxedema. This is a different change called exophthalmos. And this is it right here. Now you say, well, they're just opening their eyes. No, no. What happens here is there's a lot of fat that develops behind the eyeball and actually pushes it out like that. And you know, that'd be hard to miss as a practitioner unless you were just looking at your notes and saying, how are you today? And some practitioners do that. I'm joking of course. But certainly this would be easy to catch. And actually what's going on here, this is the patient before treatment. This is that same patient what, after treatment. Not the next day but, you know, six months down the line. Because it didn't get this way overnight, it's not going to be fixed overnight, which makes sense. But how do you treat this? Remember, underactivity is easy to treat. How do you treat hypofunctioning of any endocrine gland? Give them the hormone. How do you treat overproduction? Well, somehow you've got to inhibit that. For those of you that are contemplating doing the thyroid study on mice, there are chemicals that we're going to use on these mice, which actually prevent the binding of iodine to the thyroglobulin. And so think back in a moment, what are thyroid hormones made off, what are they contain, what are they require? Iodine. If we can prevent that connection, then we prevent the production and therefore the release of this hormone. So there are chemicals. There are drugs which can block the formation of thyroid hormone and therefore reduce the symptoms of Graves' disease. However, I'm sure if you're thinking ahead, this could be– well, this could be tricky, because what if you take too much of that drug I just named? Then you go from hyperthyroid to what, hypothyroid, which is just the reverse and it's no more fun than hyperthyroidism. So managing endocrine abnormalities is a tricky thing. And we need say nothing more than insulin to remind you of that. Insulin is controlling diabetes in some cases insulin-based. And is that a tricky hormone? Yeah, because you can go, you know, up and down that roller coaster. So anyway, let's move on. There's a third and rather surprising– well, maybe not surprising but at least curious case in the thyroid, which is fundamentally hypertrophy of this gland. Hypertrophy means getting large as you know. And the name for it which is a common name and when you've heard goiters. Now you would assume that if a thyroid is big, it's probably cranking out too much what? Thyroid. So you would connect logically a goiter with hyperthyroidism. But that's not always the case. You can have a goiter and have hypothyroidism or you can have a goiter and have hyperthyroidism. So a goiter per se is neither automatically hyper or hypo. It may be one of the other but not in an obligatory fashion. Now here's a photo

of somebody's neck. And unless you missed that day in med school, you're not going to confuse that. You're going to say, well, ma'am, you have a sizable, G word, goiter there. And so you would investigate obviously their thyroid levels and start getting involved. It turns out that at least worldwide, the most common cause for a goiter is something stupid, something very easy to fix, and that is low levels of what? Iodine. And why is that stupid? Maybe that was an inappropriate word, but we know that thyroid hormone requires what? So, we should be as nutritionist mindful of having some intake of what? In fact our government got hit to this a long time ago. That's one good thing government has done. But if you go down the aisle of a grocery store, you'll see salt, right? And here's your choices. Well, actually there's many now. We got kosher, you got sea salt, all of which you're going to pay way more for. And then you've got salt and then you've got iodinated or ionized– I can't even say that.

>> Ionized.

>> Steve Langjahr: Ionized. Well, that's not ionized, it's–

>> Ionized.

>> Steve Langjahr: Yeah, that's it. Anyway, they had different labels. They cost exactly the same. But you have a choice. You might go for kosher. You might go for organic. You might go for sea salt. And incidentally almost all salt comes from the sea, so that's just a marketing thing. But all right, why would you choose salt with iodine? Well, there's you answer. And not only would that be a good choice but government's gone beyond that. They say, well, let's put in flour too. And so, what's my point. Our goiter is common in the USA. No, never see one, at least as result of that. But are they common in inland countries, let's say third world countries, away from marine or oceanic food sources? Yeah. So anyway, it's an easy thing to fix. Sometimes it can be due to too much TSH, which is actually therefore pituitary tumor that requires a little more intervention. And Graves' disease, which is an interesting thing, we mentioned it previously. Graves' disease is actually an autoimmune disease where the immune system produces an antibody, which actually acts like TSH, by pure coincidence. So, this is kind of a complicated story. But if the immune system makes an antibody, which accidentally resembles TSH, then obviously it's going to stimulate the thyroid. So anyway, these are some of the complex syndromes associated with the thyroid. Now we're not going to get far into this but let's at least open the door to the adrenal cortex. Because we mentioned it earlier, what's that hormone from the pituitary which triggers at least some of these? A-C-T-H. So, we've got that connection already established. Interestingly and maybe horrifically, the adrenal cortex is not a simple gland. It's actually– Well, the adrenal cortex has three layers which you might recall from anatomy. I don't want to bother you with the name. So OK, they're all steroids and here they are. The first of these categories are mineralocorticoids, a wordy or lengthy statement, mineralocorticoids, let's try to dissect this, "oids", what do you suppose "oid" means? Let's just look right up here, "oids" means what? Steroids. Mineralocorticoid is an attempt to put together a lot of ideas. Apparently this is

a hormone from the adrenal cortex, which has an affect on minerals, specifically sodium and potassium. And as we'll learn in moments from now, aldosterone is the primary example of a mineralocorticoid. Then we have glucocorticoids, implying what, what's the implication, what's the word– the first part of this word, gluco, glucose. So this is very important in carbohydrate metabolism as we'll see. And third, somewhat disjointed from these, androgens. Androgens are male hormones including and mainly testosterone, which of course is a steroid. So, without getting any further into specifics, what are the actions of these hormones? We mentioned a minute ago that the most familiar and important of the mineralocorticoids is aldosterone. You already know all that you need to know about that, because you know the renin-angiotensin mechanism and therefore you know its main effect is to regulate sodium chloride, watery absorption, and also potassium secretion by the kidney. So obviously this hormone targets the nephron and controls these electrolytes specifically and water indirectly. Then there are glucocorticoids. We mentioned the name gluco has something to do with sugar. The best and main example of that is cortisol also called hydrocortisone, which you may know. And this has an interesting variety of functions or action. First all, it increases proteolysis. What does that mean? Proteolysis, lysis to– So proteolysis means to break down protein, which sounds like a bad thing. And what do you get when you break down protein? You get free what? Free amino acids. Now how could that possibly be good? Well, are there times when we need to generate a supply of amino acids in order to repair something? So this is somewhat paradoxical. How is it paradoxical? Where are we getting these amino acids to repair something? We're getting it from protein. So, why is that a paradox? We're breaking down something here, so that we can what? Build something up there. So it's weird but that's the action. Another action is lipolysis, which makes more sense, what is the word mean? Lipolysis breaking down fat. What do you get when you break down fat? You get fatty acids and glycerol. The latter can be converted straight away to glucose and the former can also be used for energy. So would this hormone be useful so far in repairing things? Indeed cortisol is often described as the body's most important stress hormone, stress hormone meaning helpful to combat stress, whether it's physical in the form of infection or even emotional which can lead to destruction around the body. But even with that said, the most important action of this hormone, I should say the most useful medical application of this hormone, is an antiinflammatory agent. So if you've heard of that hormone at all and you may have actually used it, because you can get this hormone over the counter, without a prescription, not as a pill but you can get it as cream or an ointment. And when and why would you want to use this hormone, basically because it's, what, antiinflammatory. And it's available without a prescription at least in a topical form. You can't get the pills, at least not without a prescription, because if taken in excess, this hormone has a dangerous and certainly nasty side effect. What's that? Immunosuppression. With that said, our athletes sometimes prescribed, our people with arthritis sometimes prescribed cortisol. And does that reduce inflammation of their joints and therefore give them more mobility and better health and happier life and all of that? Well, that's all

great and fine, but taken in the long run, is there a danger, is there a side effect of this therapy, and that's immunosuppression. So, it has to be carefully monitored. We'll finish with this. The androgens are represented mainly in both genders by testosterone. And the name of course testosterone implies its primary source, where it is most of the testosterone come from in at least men, the testes. But woman make testosterone too here in their adrenal cortex. It is noted for, famous for its anabolic effect. Anabolic effect because it stimulates what, it stimulates protein synthesis. And mostly that means muscle growth. And so, this takes us back to an earlier remark, why do men have more muscle? More testosterone. Why they should have more muscle is not a question I want to address, but nevertheless it's testosterone-based. But testosterone also affects the brain in both genders. Yes, it promotes what? Libido. Libido is the fancy name for sex drive. And so, if a man or a woman comes into a clinic and says, you know, I just don't have any sex drive, chances are we're going to check right of the bat what? Testosterone. So, let's leave it at that, quite a bit for one day. And hopefully we'll have some time to look at this and we'll see you Monday. Hope you have a great prosperous, enjoyable Thanksgiving. Don't forget to turn in these things so I can decide or understand what you're having in mind for your project.

>> I'm just going to ask you, what do these say?

>> Steve Langjahr: That says adenylate cyclase, which is an enzyme– well, actually an activator of this enzyme, adenylate cyclase.

>> OK.

>> Steve Langjahr: You don't to worry about it, at least not for this course. But essentially as you can see, this is at least a two-step process where this is kind of one-step process. So to summarize, hormone attaches to receptor, receptor activates an enzyme, converts ATP to AMP and then whatever is going to happen will happen. So, it's AMP, which is really completing the job of the hormone hence it's called the second messenger. And why is that? Well, because the hormone being water-soluble doesn't have immediate access or easy access. So, you might say, well, that's awfully complicated. Well, it is what it is, whereas this is a different story. It's still has to bind to receptors but those receptors are not on the membrane, they're within the target cell and therefore a change in the nuclear activity of the cell occurs. So that's the only thing to worry about.

>> Did you– Matthew said you want us to talk to him about adding him to our group?

>> Steve Langjahr: Well, since I spoke with you, he, Matthew, has recruited two other people. So they have– Actually, you know, they have four, so I don't know what to do because I really haven't looked at all the others. Why should this be a problem? Why can't we have two groups doing this? Well, because it uses a lot of rats. And I don't know if we have enough. So, I know what we have, I just don't know how many other groups are using rats, so I'm going to

have to digest this. So for now, you know, go ahead and turn it in. I'll let you know on Monday what we can do.

>> OK.

>> Steve Langjahr: I know that puts you in limbo but I just don't have immediate answers to how to respond to that. I'd like you all to do it if you want to do it. Apparently you do. And you might say, well, let's just go out and get some rats. But you just can't do that– I mean you can, I'm sure you can find a rat in every gas station in town but we want rats that are premium rats, not your average alley rats. Does it make a difference? You bet. So–