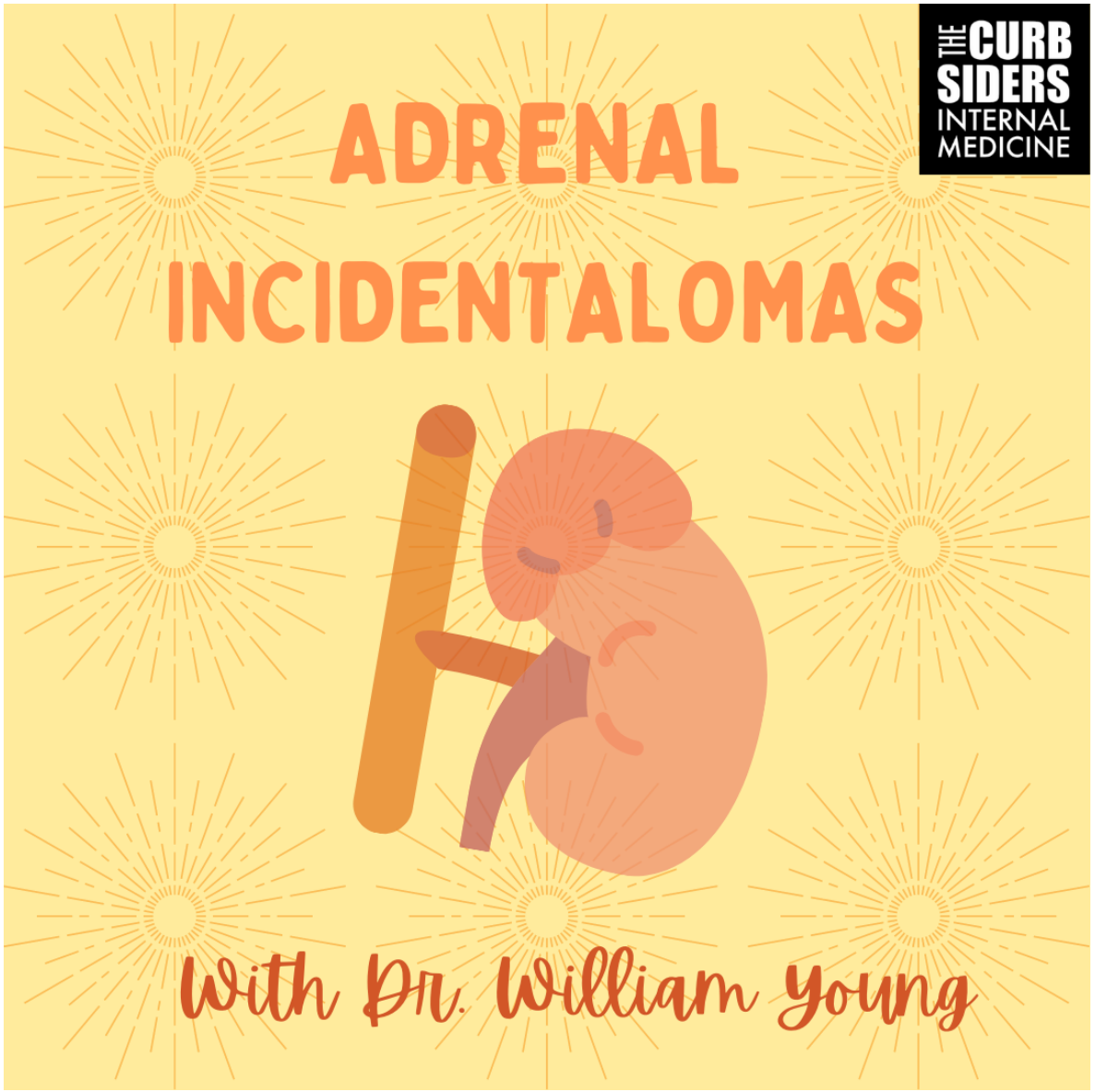
#377 Adrenal Incidentalomas with Dr. William Young



Matt: Hey, Paul. Paul, are you with me?

Paul: [laughs] Yeah, Matt, go on.

Matt: Paul, if you want an adrenaline rush, you should go camping. You know why?

Paul: Tell me why.

Matt: It's intense.

[laughter]

[Disclaimer]

[Curbsiders theme music]

Matt: Welcome back to the Curbsiders. I'm Dr. Matthew Watto, here with my great friend, Dr. Paul Nelson Williams. On tonight's show, we are going to be talking about adrenal incidentalomas with a fantastic guest, Dr. William Young, Jr. But before we get to that, Paul, will you tell the audience what is it that we do on the Curbsiders?

Paul: Sure, happy to as always, Matt. As a reminder, we are *the* Internal Medicine podcast. We use expert interviews to bring you clinical paroles and practice-changing knowledge. I will also take liberty of mentioning that we are joined by cohost, super producer and my future boss, Malini Gandhi, who put this tremendous episode together. Malini, how are you?

Malini: I'm well.

Paul: Glad to hear it.

Matt: A reminder that this and most episodes are available for free CME through VCU Health at *curbsiders.vcuhealth.org*. Now, Malini, can you please tell us about our wonderful guest.

Malini: Yeah. We had a really great conversation today with, Dr. William Young. He is the Tyson Family Endocrinology Clinical Professor and Professor of Medicine in the Mayo Clinic College of Medicine and Science at Mayo Clinic in Rochester, Minnesota. He is the recipient of multiple education awards and is a past president of the Endocrine Society and past chair of the Division of Endocrinology at Mayo Clinic. His clinical research focuses on adrenal and pituitary disorders. He's delivered more than 900 presentations at National and International meetings, and he has been an invited visiting professor for more than 150 medical institutions.

So, today we had a really great conversation with him about how to distinguish benign from malignant adrenal incidentalomas based on imaging, characteristics as well as the nuances of working up hormonal hypersecretions, adrenal incidentalomas, as well as a lot more.

Matt: All right, so let's jump into our first case.

Malini: The first case we have for you is the case of Mr. Matthews. He is a 68-year-old man with history of hypertension, obesity, and type 2 diabetes on metformin. He had presented to the ED two weeks ago with left lower quadrant pain and got a CT in the ED at that time that was consistent with diverticulitis, which is now resolved. However, the CT scan had also incidentally demonstrated a right adrenal mass. The mass is 3.4 cm in diameter, it's homogeneous with smooth borders and has an attenuation of 6 HU. So, you're seeing him in

your primary care clinic two weeks later for follow up. We wanted to start first, just very basic with definitions. How would you define an adrenal incidentaloma?

William: Adrenal incidentaloma is like found in similar to the case you just presented. It's found typically on computed image, which is either going to be CT, MR or PET scan. That scan was not ordered to look at the adrenal glands. So, this was truly serendipitous and you find adrenal mass. The patient cannot have signs or symptoms of adrenal disease, and the mass has to be of significant size. When I write about this, we use a cut off of 1 cm or larger.

The most common question I get after giving a presentation on adrenal incidentaloma is, what about 9 mm? What about 8 mm? The answer is it has to be a definite mass. If it's a definite mass, that's 8 mm. Sure, that's an adrenal incidentaloma, but the smaller you put that cut off, you're not sure if it's just adrenal thickening. We're not talking about adrenal limb thickening here, we're talking about a true adrenal mass. That's where the 1 cm cut off comes from.

Paul: We often like to ask folks for their scripts, how they actually talk with patients about a certain topic. When this comes up and you're trying to explain to the patient and follow up that they found something on their kidney or something on their adrenal gland, I always feel like I'm muddling the words and trying to frame it in a non-alarmist way. I feel like I actually make myself less clear. Would you mind sharing with us how you describe the initial finding where we don't quite know what's going on to a patient? Like, how do you frame that and what does that sound like when you're talking to patients?

William: Yeah, initially, this certainly can be anxiety provoking for patients, because you tell them they do have a mass. That's what it is. You can't sugarcoat that. They have a mass on their adrenal gland, but then I reassure them that the vast majorities are benign and nonfunctioning and what's very reassuring is to actually show them their mass on their scan. This is really helpful to patients to put it in perspective, so they actually can see the size and you can tell them what the equivalence is in inches and they find that very reassuring. Yeah, there's still going to be some anxiety involved. It's not like it's a lump on their arm that they can look at and push around. It's something they can't see or can't feel.

Matt: What about the imaging characteristics because we get so many follow-up appointments in primary care, someone had a CAT scan like this gentleman, and there's all sorts of incidentalomas that we're dealing with. With the adrenal specifically, what do we need to think about there? Do we get enough information from just a non-contrast CT or does it have to be a contrast CT?

William: Yeah, Matt, that's a great question. 90% of what I do with a patient with adrenal incidentaloma is based on the imaging phenotype. When I say imaging phenotype, I'm just referring to what does the mass look like. I get most of my information from a non-contrast CT because it tells you the density of that adrenal mass, and that really provides some information what it may or may not be. Contrast enhancement can help, especially if you're worried about metastatic disease, primary adrenal cancer or pheochromocytoma. All three of those are very vascular masses, and they really light up when you have contrast. It turns out the percent contrast washout is not as helpful as we used to think it was. So, we have plenty of examples, for example, pheochromocytoma that washout contrast quickly and supposedly they're not supposed to, but they can.

Matt: Yeah. I always thought that the fancy washout study was better. I was quite surprised, actually, reading about this, preparing for this episode, that it seems like the unenhanced-CT seems to be good enough. Can you dig in a little more to the specifics of, like, what reassures you or what are you paying attention to? What words should we look for when we're reading that report?

William: Yeah, so, like we just heard about, in this case, it had smooth borders. It was homogeneous. Those are two very positive factors. And then the unenhanced-CT attenuation was less than 10 HU. So, we know it's lipid rich. I tell this patient immediately, this is benign. It cannot be cancer. I don't know if it's functioning yet. I don't know if it's making a hormone, but it's not a pheochromocytoma. It's not metastatic disease. It's not a primary adrenal cancer. Now, if the unenhanced-CT density is greater than 20 HU, well, then that's lipid poor. Then that could be all those other things. It even could be a lipid poor benign adenoma.

Paul: I look forward to the point in my career when I can just look someone in the eye and say definitively, this is not cancer. I don't know that we're going to get there just because I live in anxiety land, but that would be very reassuring to hear as a patient.

Matt: So, Hounsfield units, that's the way CTs can measure density. So, less than 10 HU, that's reassuring. And it's very unusual that I think I even read that, maybe there's been no cancers documented as less than 10 HU. I don't know if that's too strong of words.

William: Yeah, I never used the word never in medicine. I've learned that over the years.

Matt: Right.

William: I'm sure somebody somewhere has a 9 HU cancer. Yes, in general we use 10 HU. Hounsfield units are just a quantitative measure of density. It's named after Godfrey Hounsfield. He actually invented the CT scan and he won the Nobel Prize in 1979 for that invention. The lower the number, the less dense. The lowest number you could get is air that's going to be like -600. The highest number you're going to get is about +1000 and that's bone. A kidney would be +20 to 60. Fat is going to be like -80, -100.

Paul: Malini, what do you want to get into next? I know this is your brainchild here.

Malini: [chuckles] Yeah, no, I think those were really, really helpful kind of framework for how to think about approaching the imaging characteristics. I think in addition to and you already brought up that other major question of whether this is functioning or not. In addition to whether this is malignant. So, I wanted to get your kind of general approach in terms of how do you think about a patient presenting with an adrenal incidentaloma? What patients should receive work up for hormonal hypersecretion and what tests should we be ordering there?

William: So, Malini, assuming there's not something else that's obvious for example, an adrenal myelolipoma, that's something that your radiologist can tell you it is. Those are nonfunctioning and usually we would not do any hormonal workup. Basically, all other adrenal masses need a hormonal workup. Now, if the unenhanced-CT attenuation is less than 10, it cannot be a pheochromocytoma. I would advise to not screen for pheochromocytoma because all that's going happen [laughs] you're going to be dealing with a false-positive test and trying to explain your way out of that unless another diagnosis is obvious. Like for example, let's say it's lipid poor, it's inhomogeneous, has cystic areas within it, that'd be high suspect to be a pheochromocytoma. I would not screen that patient for subclinical Cushing's. But basically, all other patients you should screen for something that's called “subclinical Cushing's syndrome.” All that word means is we can't see it with our eyes.

I had a patient this week, I walked in the room, she's got Cushing syndrome. I can see that. Full round red face, supraclavicular fat pads, purple-red striae in the abdomen. Subclinical Cushing's, the BMI could be 18. You can't tell by looking at the patient that they have subclinical Cushing's. All patients with incidentally discovered adrenal mass should be screened for this subclinical glucocorticoid secretory autonomy and that's done with the

baseline DHEA sulfate and a 1 mg overnight dexamethasone suppression test. Usually, I also throw in a baseline ACTH level. Those are the three tests I would do for subclinical Cushing's. If the patient's hypertensive and I think you mentioned this patient's hypertensive, they should all be screened for primary aldosteronism and that's pretty simple. It's just a morning blood test, and we measure aldosterone and renin. Renin can be plasma renin activity or plasma renin concentration.

Matt: We were having of a debate about this, Paul and I, beforehand, the testing for adrenal incidentaloma, let's say we're seeing this person for hospital follow up as the primary care, and this person has hypertension. Should we be giving the 1 mg dexamethasone suppression test and the ordering the DHEA sulfate and the ACTH? Can you tell us how can we do that in a way that is interpretable that you don't have to just repeat it like the primary care didn't do it the wrong way?

William: That's a really good question because a lot of clinicians want to just get all their tests done on day 1. You can't do that. If you're going to do an overnight dex suppression that has to be separated. I would get my baseline test in this hypertensive patient who clearly doesn't have a pheo. I do baseline, and by baseline, I typically mean 8 AM labs for ACTH, DHEA sulfate, cortisol, plasma, aldosterone, and renin. And then on the next day that evening at 11 PM, 1 mg of dexamethasone, and the following morning at 08 AM, a blood cortisol level and normal suppression would be less than 1.8 mcg/dL with the 1 mg overnight dex suppression. So, it is a two-day evaluation.

Now, I am going to clue you in on a shortcut here. The shortcut is if the DHEA sulfate is above 100 mcg/dL, regardless of age or sex, that patient does not have subclinical Cushing's. So, we all make DHEA. Now, there are different reference ranges based on age and sex. We make DHEA in our adrenals because we have ACTH. It's telling our adrenals to make cortisol, but also tells our adrenals to make DHEA. DHEA sulfate has a very long half-life, 12 to 16 hours. It's my adrenal glycosylated hemoglobin. It's not like this, that's ACTH going up and down. It's flat. It tells me have the adrenal glands been seen ACTH the last couple of days.

If DHEA sulfate is low, less than 40 mcg/dL, that suggests that your patient may have subclinical Cushing's. Whereas if it's above 100, very unlikely that patient has that subclinical glucocorticoid autonomy. When the DHEA sulfate is above a 100 and this was a long tip, I don't do an overnight dex suppression.

Matt: Yeah, that's a test that it hadn't been something that I've been ordering. We talked to somebody about PCOS, and that was part of the work up that she had recommended for that, but I hadn't really been familiar with it as part of the work up for incidentalomas. This is helpful that you're telling us the purpose of getting that testing because I always have to look up that diagram of the cholesterol and the hormones and the pathway, all the different enzymes that can go wrong. Okay, so basically, let me recap a little bit and then we'll jump off from there. When someone has an incidentaloma, it's like we're thinking, is this malignant? Could this be malignant and is this functioning? Those are some of the important things to ask. Everybody should have a dexamethasone suppression test because this subclinical Cushing's is-- we should think about Cushing's for everyone, because this subclinical Cushing's seems to be pretty common.

If the person has hypertension, we would think about primary aldosteronism, and we would check the aldosterone and renin as well. Then the testing for Cushing's you said was the baseline DHEA sulfate and cortisol. Depending on those results, we may or may not do a 1 mg overnight dexamethasone suppression test and see if that cortisol is below 1.8 or not. You gave us the cut off DHEA sulfate above 100. We don't have to do that dexamethasone suppression test.

William: This concept about DHEA sulfate was published many years ago and then it was a very nice study that came out of the UK about two or three years ago. Just last year, we published a study from our center at Mayo Clinic that documented this phenomenon.

Matt: Okay, Paul, so what do you think? Are you going to be ordering any of this workup? I know you had questions about referrals and things like that.

Paul: It's one of the things where I probably will now, that I feel a bit more comfortable hearing those things, I will order those things, but I will have low threshold to be calling my friends in endocrinology. These are the types of things that make me panic. I might do something wrong and do something horrible. So, yep, I'll order them.

Matt: Yeah, I find that I get these concepts. It helps me in two ways. Number one, I feel empowered to order these tests, but oftentimes the first time I order them, I want to talk to somebody about them that knows more than I do. Number two, if these tests are done to my patient, I understand what's going on in my patient. It gives me more street cred when my patient's talking to me, and I'm like, “Oh, yeah, I understand what they did and why they did it, and I can explain it to them.” I think this is super useful, even if you're not going to pull the trigger and do the testing yourself. I think sometimes it just takes a while to get in to see specialists, and it's good to have some of the workup going ahead of time. So, Malini, where are we headed to next with this case?

Malini: Yeah, so we have some lab values for him. So, as he mentioned, given that hypertension, we ordered the aldosterone and the renin, given that we want to consider subclinical Cushing's in everyone, we also ordered the DHEA-S. We did not know the parole yet about how you didn't have to get the overnight suppression test if you had that DHEA-S. So, we ordered that right away. Given his imaging characteristics of the Hounsfield units of less than 10, we didn't screen him for pheochromocytoma. So, we get these lab values back. His renin is nonsuppressed and his aldo-to-renin ratio is less than 20, so it doesn't look like a primary hyperaldo picture. However, we do find that his 1 mg overnight dexamethasone suppression tested as normal, the cortisol greater than 1.8, and then his DHEA-S is low. So suggestive of possible subclinical Cushing's syndrome.

William: Yeah, Malini, that's interesting. Now, if we did get the DHEA sulfate back and it was low, I would go ahead and do the overnight dex. So, yeah, you have a perfect workup there. The overnight dex suppression is a screening test. The DHEA sulfate is a screening test. I don't think, but this is controversial if you ask me to make sure I say that when I bring up a controversial issue. This is controversial because what happens down the road is this patient could go to surgery because the overnight dexamethasone suppression test is abnormal. I would never send a patient to surgery based on a 1 mg overnight dexamethasone suppression test. Why is that? Because of the high false-positive rate with a 1 mg overnight dex, especially in people who are overweight.

So, in a patient like the one you just shared with us, did that suppress with the 1 mg overnight, I would confirm that. And how do you confirm it? You give 8 mg of dexamethasone at 11:00 PM, you measure cortisol the next morning. 8 mg of dexamethasone is 15 times more glucocorticoid than a human makes in a day. The cortisol the next morning in a normal person will be 0. Anything we find in this person who has an 8 mg overnight dex, anything that's detectable in cortisol is what this adrenal nodule is making autonomously every minute, every hour, 24 hours a day. That's what I would use to then direct next steps in management, where then I'm not worried about a false-positive test, but not everybody does it that way.

Matt: Malini, our patient had, what was their morning cortisol value? Was it less than 1.8 or it was inappropriately--

Malini: Yeah, the cortisol was high, greater than 1.8. Sorry, I might have misspoken, and I apologize if I did.

Matt: No, these things are hard for me to think through out loud. So, I think we'll keep this in, so the audience is following with my clarifying question. Okay, so this person did not suppress, but we looked at them when went in the room, and they didn't have the moon face, the purple striae, the supraclavicular fat pads. So, we're thinking this is the subclinical Cushing's. And how common is that? I saw some numbers out there, 30% to 50%. Could it possibly be that high for these patients with the incidentalomas?

William: Yeah, if you're just using the 1 mg overnight dexamethasone suppression as your screening test, it could be as high as 30%. If you're doing the 8 mg overnight dex, we're talking more like 8%. In other words, there's a lot of false positives with that 1 mg.

Matt: And then another follow-up question, because this was such a new concept to me, the subclinical Cushing's, why should people care about it? Are there bad outcomes linked to it? How do we follow this over time?

William: Well, Matt, the way I explain it to patients, it's as if their adrenal gland is dosing them with 1, 2, 3, 4, 5 mg of prednisone that's distributed evenly over the 24 hours. I tell them, look, as a doctor, I would never give you 4 or 5 mg of prednisone for no good reason but your adrenal gland is. Could that be contributing to your high blood pressure? Could it be contributing to your hyperlipidemia? Could it be contributing to your hyperglycemia? Could it be contributing to your body weight, could be causing osteopenia? Osteoporosis? The answer is yes, it could. The problem is I can't prove it. We don't have a way of proving that this glucocorticoid secretory autonomy is actually causing any of those morbidities that the patient has. But then I also tell the patient, again, these are patients who've had absolute confirmation of this subclinical autonomy with an 8 mg overnight dex.

I tell them that this isn't going to go away, this is going to continue, and it does slowly increase over time. Again, your adrenal nodule is benign. It's not cancerous, but it will slowly enlarge. It got to be 3.4 cm somehow, and it's going to slowly get bigger over time. As it does, the factory is bigger. It'll make a little bit more cortisol over time. So, this isn't going to go away. It's only going to progress. That's the rationale for thinking about doing something. Now, obviously, there're a lot of other factors in every patient's case. The younger the patient, the more aggressive my recommendations, the older the patient or with a lot of comorbidities, I might be a little more cautious on being aggressive. Everything I'm telling you tonight is assuming you have access to an expert laparoscopic adrenal surgeon.

Paul: And for these patients if you discover that, so for instance, in our patient, who is let me just backtrack here, a 60-year-old gentleman who I might not necessarily be thinking, say, DEXA scanning, if you discover subclinical or you suspect subclinical Cushing's and they're getting this low-grade steroid exposure, is this someone that you might actually refer for, like DEXA scanning look for osteoporosis or osteopenia, is that part of your workout for these patients?

William: Yeah, Paul, absolutely. They all should have a bone marrow density. Once you've documented this subclinical autonomy, they should have a bone marrow density test, because that may actually put you one way or the other.

Matt: So, we talked about testing for Cushing's and we're going to talk a little more about

aldosterone and renin testing. This patient, we didn't give you characteristics that would make us think of pheochromocytoma, but if it was an adrenal nodule that was greater than 10 HU or had other imaging characteristics making us think of a pheochromocytoma, what would that testing look like because you mentioned you don't want to order it if you don't need to? What's a positive test to you and how do you order it?

William: Yeah. Boy, Matt, there're a lot of caveats in this. Now we're going to be talking about a lipid-poor adrenal mass. One of the most important caveats is the size of the mass is important when we're talking about lipid-poor adrenal masses. If it's less than a centimeter and a half, our most sensitive test, plasma fractionated metanephrines may be normal in a patient with a pheochromocytoma. Unlike an aldosterone-producing tumor, that can be 4 mm and cause the whole syndrome. For a pheo, the factory needs to be pretty big before it's biochemically detectable. And now that so many individuals are getting cross-sectional imaging for lots of different reasons, we're stumbling over asymptomatic pheochromocytomas. But even more importantly, prebiochemical pheochromocytomas. In other words, they're a centimeter and a half and our lab tests are normal. You have to have a high degree of suspicion for pheochromocytoma based on imaging phenotype.

The imaging phenotype is lipid poor and if contrast was administered, they light up like a lightbulb. They really enhance with contrast. Now, most pheochromocytomas that are 3 cm or larger are easily biochemically detectable and in the patient with the lipid-poor adrenal mass, my test of choice would be plasma fractionated metanephrines. It's the most sensitive biochemical screen we have.

Matt: Oh, good. We don't have to mess around with the 24-hour urine.

Paul: I have the same reflex response, Matt.

Matt: We were talking about imaging before, just to say it out loud, unenhanced CT can be an okay way to detect some of these. And then you said that the CT with all these fancy washout studies is not as helpful as we used to think it was. There's MRI and MRI test because sometimes I feel like this happens sometimes where we'll have a CAT scan and then the radiologist asks for another CAT scan maybe with some attention to the adrenals or an MRI. Can you just talk about that? Is there any preferred tests that we should get as follow up to an initial?

William: Usually what it is, is the patient had a contrast-enhanced scan as their only scan to begin with, whether it was a CT chest looking for a PE or something. And then we really do need some measure of the lipid status of the mass. That's either going to be on an unenhanced CT or it could be an MR with chemical shift imaging. It tells you the same thing, the lipid content of the mass. MR or CT would be equivalent in that regard.

Matt: That's probably what it is. I hadn't made that connection. It's probably the contrast-enhanced CT that I'm getting. And then they're asking me for a follow up. We do have another case that we want to get on to in talking about aldosterone. Paul, anything else from this first one? Or Malini, anything else from this first one that you think? Paul, you look like you're going to say something.

Paul: Oh, I mean, that's just my face, Matt, you know that. I'm just always vaguely uncomfortable, [Matt laughs] Even in the absence of biochemical activity and even if the characteristics are almost entirely benign. I guess I can't remember if we talked about a size threshold where you would still be referring to surgery. Like, is there a time where you would still surgerize a patient, even if it sounds like it's, because as you say, these things had to come from somewhere and presumably they're growing in size. Does any of this warrant surgery even if they're biochemically boring and radiographically not that interesting?

William: That's a really good question. The size threshold has some basis in fact. Unfortunately, it gets misused and everyone focuses on size rather than imaging phenotype. In other words, a lipid-poor 2 cm adrenal incidentaloma really, really concerns me whereas a lipid-rich 5.5 cm adrenal incidentaloma does not concern me. It's benign. It's big, it's benign. That 2 cm lipid-poor mass that maybe malignant, it may be a pheochromocytoma that deserves our attention. A couple of years ago, we looked at our experience over about 15 years with 4000 patients with adrenal masses. All of those that had adrenal masses greater than 4 cm, 50% were something bad. So, that's where that 4 cm data comes from, it's real, it's true. But on the other hand, half of them over 4 cm were not something bad. 22% or so were pheochromocytoma and about 31% were cancer, either primary adrenal cancer or metastatic disease. But that's where that 4 cm cut off comes. I'd come back to what's, the imaging phenotype? Yeah, if it's lipid-poor greater than 4 cm, you bet that's coming out. There's no way that should stay inside that person's body. But if it's lipid-rich--

Matt: I guess that begs the question of like, follow-up imaging, because if it grows big enough, I guess eventually could cause compressive symptoms. Is it standard to get scans every two years, five years, something like that?

William: Yeah, yeah, that's a good question. Well, it does come back to the unenhanced CT attenuation. Those lipid-poor masses either need to come out or followed closely. People ask me, “Well, how long do you follow a lipid-poor adrenal mass?” And I would say, “Forever.” They can't be anything good. If you're going to follow them, you're stuck. You're going to follow them forever. Whereas I think what, Matt, you're asking about is the lipid-rich mass. I tell people to get one more scan. If it's lipid-rich, there's no rush to repeat your scan. Get it in a year. If you're worried about radiation exposure, do an MRI, it doesn't matter. You just want to make sure it's not growing under observation and that the radiologist was correct the first time around because I've seen this.

I mean, I'm comfortable looking at these masses and ignoring what a radiologist says. But a lot of clinicians who aren't looking at adrenals, they rely 100% on what the radiologist says, and trust me they're not a [unintelligible [00:32:09]. [laughs] So, I think all these patients for the lipid-rich deserve one more image a year later. Now, that's different than, for example, the European clinical practice guidelines. They say if it's lipid-rich, never scan them again. That's not what I personally do and that's not what I advocate.

Matt: For our patient, this 68-year-old lipid-rich, it's 3.4 centimeter I believe, based on our biochemical testing, we said this person has subclinical Cushing's. Is there a follow-up biochemical testing that you would perform on this person as well because can that become clinical Cushing's eventually? Or I guess we already know. I guess clinical Cushing's, would you have to see it. I kind of answered my own question, but what do you do, how do you follow it? Is there any lab testing that you would follow for this person?

William: If the decision is to follow this, then yes, I think it's reasonable to get repeat baseline studies in a year. I might even throw in a 24-hour urine cortisol excretion along with the baseline cortisol, ACTH, DHEA sulfate, and then 8 mg overnight dex. There is a risk that this can get slowly worse with time. The conversion rate to clinical Cushing's is very low. It's around 4%. It can happen, but it's a low risk.

Matt: Okay. All right, so I think we should move on to our next case. This has been extraordinarily helpful so far. We have another high yield scenario for you.

Malini: This is a case of Mr. Jones. He is a 58-year-old, has a history of hyperlipidemia and poorly controlled hypertension and refractory to multiple medications, blood pressure of 148/92 currently, and he too was found to have an adrenal incidentaloma at similar imaging

characteristics to that of Mr. Matthews. However, unlike Mr. Matthews, his DHEA-S was normal. So, we didn't get the overnight dex suppression test. But when we got his renin and aldo levels, his renin was suppressed and his aldosterone level was high. So, we wanted to talk to you a little bit more with this case about primary hyperaldosteronism and the nuances of testing and managing that. I guess to start with one question, this is a guy who's obviously has hypertension, is likely on lots of blood pressure medications. Should any of those be held when we're assessing for primary hyperaldo in terms of getting the lab tests? So, any of those blood pressure meds mess up the lab tests?

William: What I'm going to tell you also is a little controversial and a little contradictory to the 2016 Endocrine Society Guidelines, for which I was a co-author, which advises replacing any medications that could interfere with the renin-angiotensin-aldosterone axis. In other words, if the patient was on an ACE inhibitor or a thiazide diuretic, the guidelines advise replacing those. I'm personally convinced that simple step is preventing clinicians from testing for primary aldosteronism. In those guidelines, we advise that all patients with resistant hypertension be tested for primary aldosteronism, 100% of them.

There was a nice study out of Stanford. They had like 100,000 patients in their system with hypertension, and they had 4660 with resistant hypertension. All of them should be tested for primary aldo. Only about, I think it was 2.1% were tested for primary aldosteronism. Another study from the University of Chicago, again, about 100,000 patients they looked at. What was the screening rate for patients with hypertension and hypokalemia? In those guidelines, we said everyone with hypertension and hypokalemia should be screened for primary aldo, and it was 2.7% were screened for primary aldo.

We have a major problem in the United States that clinicians are not testing for primary aldosteronism. I think there're a lot of reasons for it. One of them is this nonsense about drugs and not knowing what to do with drugs. My approach and what I've written online and in print is, “Don't worry about drugs. Don't stop drugs, just test. Nothing causes a false-positive test.” So, you have to use a cut off for aldosterone. We recommend 10 ng/dL, cut off above 10 ng/dL with a plasma renin activity less than 1 ng/mL/hr or plasma renin concentration less than the lower limit of the reference range, which typically be around 8 depending on your particular assay. That's a positive case detection test.

The point about primary aldosteronism, if your patient truly has it, it's hard to make renin budge despite ACE inhibitor, diuretic, ARB, spironolactone. It's hard to make renin rise. But that's the concern everyone has that these drugs will cause renin to rise. I tell people what's the worst thing could happen. Okay, renin’s 3. Well, now you can stop the potentially offending drugs, wait two weeks and retest if you want to do that. Usually that patient with renin 3 doesn't have primary aldosteronism.

Matt: I love this point and we've talked about this on the show before, but just probably not everyone heard that and I need to refresh myself as well. If somebody who's just hypertensive doesn't have primary aldosteronism, what would you expect their renin and aldosterone to look like when you tested them.

William: The normal relationship between renin and aldosterone is about 10 to 1. If you're talking about plasma renin activity assay, if you're talking about direct renin, it's more 1 to 1, but it's about 10 to 1. The reason we make aldosterone is we make renin. If I'm on a low-sodium diet for the last three days, I'm going to make more renin to defend my volume, and my aldosterone will be higher. If my renin is 6, aldosterone will be 60. That's normal for someone on a low-sodium diet. There is no normal range for aldosterone, it's what's aldosterone with respect to renin, it's that relationship.

Matt: When somebody is on blood pressure medication, you said it's not going to cause a

false positive. So, what would you expect just somebody that's on your standard anti-hypertensive, what would you expect? The renin should not be suppressed you're saying. If it's a patient who has hypertension, they don't have primary aldosteronism, what would the renin and aldo look like there for someone that's one or two meds?

William: Let's say the patient is on 20 mg lisinopril and 25 mg hydrochlorothiazide. What happens with lisinopril is renin will go up and aldosterone will go down, and with hydrochlorothiazide, renin will go up. I get this phone call and email a lot, “Oh, the renin is 25.” My first question is, “What drugs are the patient on?” Well, ACE inhibitor. Well, that's what it should do. It's blocking [laughs] the action of renin, so renin goes up.

Matt: The primary aldosteronism, I think it's helpful to understand what's normal, what would it look like on meds, and then what does it look like for this person who has this autonomous production of aldosterone?

William: Those medications are important because it's actually powerful information. If renin is low and the patient is on an ACE inhibitor and a diuretic, why is it low? It's low because they most likely have primary aldosteronism.

Matt: And that autonomous production of aldosterone is suppressing the renin.

William: It's been suppressing renin, yeah. It is our most common cause of secondary hypertension, 5% to 10%. And those are low estimates these days. There have been some recent studies that suggest the prevalence much higher than that.

Matt: One last question about this, because this was something that I saw reading some of these papers, was that if you treat somebody who has primary aldosteronism and initially their renin was suppressed, is it true that as you get adequate treatment or adequate levels, you may see the renin start to rise up?

William: Yeah. Matt, you read a lot and good stuff.

[laughter]

Paul: He sure does.

William: When we treat a patient with primary aldosteronism, our goal is to block aldo from working with spironolactone or eplerenone, and you know you've blocked aldo from working when aldo can't activate the receptor, cause sodium reabsorption, volume expansion, suppression of renin. So, when you see renin starting to rise, you're doing a good job, you're blocking the MR.

Matt: Yeah. This is a topic that I guess Paul, what was this like 300 plus episodes ago, Dr. Topf, our friend, he's a nephrologist who treats a lot of refractory hypertension, resistant hypertension, told us about this, he was saying that mineralocorticoid-receptor antagonists for a lot of these patients with resistant hypertension, it would seem to work.

William: It's like magic.

Matt: Yeah. You can even sometimes start to peel off some of the other medications in those cases. Part of why we wanted to talk to you about this topic is when you order this testing, sometimes I see a suppressed renin, but the aldosterone is like 7 or 8. It's not greater than 10, it's not greater than 15 or 20, which I would have classically thought. How good is that test and are we ordering it wrong maybe? Do you think there're other reasons why we might just not get that classic picture when we order it?

William: The only rule is it should be a morning blood test because aldosterone levels fall through the day in patients with aldosterone-producing adenomas. That's the only rule. Having said that, this is a poor case detection test. Sensitivity and specificity about 75%. This is not a great case detection test. If I got a case like the one you just mentioned, patients on an ACE inhibitor and a thiazide diuretic renin's low, aldo is only 7, I'm worried about that. Why is renin low? And I actually would go ahead and do a 24-hour urine on a generous sodium diet for aldosterone, sodium, and creatinine. If the urine aldosterone is above 12 mcg and the sodium is above 200 mEq. If sodium is about 200 mEq that patient is volume expanded. There's no reason to make a renin, no reason to make aldo. Aldo should be less than 12 mcg. But if the aldo is above 12 mcg in a 24-hour urine with volume expansion in a patient with low renin that's primary aldosteronism, despite the plasma aldo of 7 ng/dL.

Matt: Yeah. So, you give them instructions to eat a high-sodium diet. Just you tell them to add salt to every meal they eat a couple of days before or something?

William: Yeah. I basically tell them, “Look, for the next three days I want you eating pickles, potato chips, pizza, popcorn, McDonald's fries, fast food.” Now there are some people say, “I can't do that.” These people actually been doing a good job with a low-sodium diet. In those instances, I give them sodium chloride tabs, 1 g tabs 2 tabs 3 times a day with food. Don't do it on an empty stomach, it causes nausea. That gives them about 100 mEq of sodium. If they can get another 100 mEq from their diet. We actually have a patient education for sure that clues them into where a lot of the sources of sodium are in the diet. It's pretty easy to put together a high-salt diet.

Paul: I'm pretty sure that every Monday morning I'd be ready for my 24-hour urine aldosterone-

[laughter]

Paul: -to describe what I ate from Friday through Sunday. I might just check this for fun.

Matt: Paul, I worry about you.

[laughter]

Matt: This is really helpful because I had read as well that single measure of an aldosterone is not necessarily reliable and you might want to investigate further. I guess the question is, if we do think we have a case and we're sending them, what do we do from there? What do you recommend we do? Is that a time to refer? I think we could order this test in primary care, make sure they just get them done in the morning and send them to you, I guess, regardless of what the results are if we don't understand what to do next.

William: Yeah, I think endocrine referral, I'd have a low threshold for that. I really would.

Matt: Let's say it's an older patient. I mean, empiric treatment with an MRA, mineralocorticoid-receptor antagonist. Sometimes I have done that. Patients are on three meds for blood pressure. We do this testing, it's positive. I often will start the medicine. I still refer to either nephrology or endocrinology just for further evaluation. But I've heard some horror stories about people just like not starting that agent for further workup and then something bad happens if that person you don't see them for a couple of years.

William: Our preference is to fully work the patient up if we can in the first instance because once you start spironolactone and you get them on a good dosage so that now renin is

detectable, you're out of luck. You can't do any more testing for primary aldosteronism. You can't do adrenal vein sampling if it went that far. In our words, we'd have to stop spironolactone, wait four to six weeks, and then reassess.

So, in general before starting the MR antagonist, we'd want to complete our evaluation. But let's say, like I think you said it's an older patient, poorly controlled hypertension, maybe the potassium is at the low end of the reference range. You get an iffy plasma aldo of 6 with a low renin. Sure, you could add spironolactone. That's a great antihypertensive drug and as is eplerenone. Eplerenone is shorter acting, so it has to be twice a day. Spironolactone is long acting, so it could be once a day. But yeah, it's a fantastic antihypertensive drug class.

Matt: It just seems like this is such a large number of patients and the workup beyond this, like, adrenal vein sampling, do we have the infrastructure in place to test all these patients and potentially get them a curative surgery? I know that's the goal is if we could cure their hypertension or make it much easier to manage with the surgical procedure. What are people saying about that in the field?

William: Yeah, a timely question. This came up today during our Task Force Zoom discussion on the next Endocrine Society Primary Aldosteronism Guidelines that we're just starting right now. And everyone brings this up. If we actually started diagnosing primary aldo, we could overwhelm the systems. My comeback is I'll look forward to that day. [laughter] I will relish it when it happens, because people have been saying this for a decade, and it's not happening. When it happens fantastic. Right now, we only do about 100 adrenal vein sampling cases a year here. We could easily do 600 a year. We have capacity at a place like this. Now, obviously, every place wouldn't have that capacity.

And you're exactly right, if clinicians started testing for PA and pursuing its evaluation, it definitely would overwhelm some systems. We are going to need predictors early on, “Is this patient likely to have unilateral adrenal disease and be a great candidate for surgery, or patient likely to have bilateral adrenal disease and we're going to treat him with spironolactone or eplerenone anyway?” So, those studies are going on right now with the hope that someday we can actually use that information to direct which patients go on for that further subtype evaluation.

Matt: Bill, so I wanted to ask about the most common cause of this primary aldosteronism. What should we think about because you mentioned you're not always sure if it's a unilateral nodule or not?

William: In fact, Matt, usually it's not a unilateral source of aldosterone. About 60% of patients both adrenal glands are making too much aldosterone. We call it bilateral hyperplasia. We still don't understand the underlying pathogenesis in most of those cases, whereas about 30% have a unilateral aldosterone-producing adenoma. We do understand the pathogenesis of those patients. They actually have a somatic mutation that's predisposed that patient to develop an aldosterone-producing adenoma. So, yes, the majority have bilateral disease, which we would treat medically with MR antagonist. We do not recommend bilateral adrenalectomy if they have bilateral disease. It's just not a good trait, [laughter] now they have to take aldosterone pills and cortisone pills, so we treat them with spironolactone or eplerenone.

Malini: Yeah, and speaking of bilateral disease, just going back to our original imagery and original case, for all of the cases we've given you so far, the patients have all had a unilateral adrenal incidentaloma. Let's say Mr. Matthews or Mr. Johnson had had bilateral adrenal nodules from the beginning. What would you be thinking there as a primary care doctor? What should your next step be?

William: That's a different kettle of fish, so to speak, because now the differential is different. It could be underlying congenital hyperplasia. It could be bilateral myelolipoma, bilateral pheochromocytoma, adrenal lymphoma, metastatic disease. I mean, the differential becomes much more broad. I think you could make a case for the patient with bilateral adrenal masses, maybe rather than trying to start a workup to basically refer those patients to an endocrinologist in the first instance.

Matt: In my experience, I don't remember many patients where I've discovered bilateral adrenal problems outside of, like, I already knew they had a cancer, and then I was like, “These are metastatic.” This is metastatic. But otherwise, that would be unusual enough, I'd be like, "I need to send this person on their way."

Paul: Yeah, I'd pull the report pretty quick if that was the finding that came back to me.

Matt: All right, well, this has been so fantastic, and we can't thank you enough for your time. Can you give the audience a couple take-home points that you really want them to remember from this interview?

William: So, 95% of adrenal incidentalomas are benign. That's a big take home point. And about 85% are nonfunctioning. The most common autonomous function is cortisol, and we call that subclinical Cushing's syndrome. All patients should be screened for subclinical Cushing's unless another diagnosis is obvious, like pheochromocytoma. We screen for subclinical Cushing's with baseline cortisol, ACTH, and DHEA sulfate.

If DHEA sulfate is greater than 100, typically we don't need to do overnight dex suppression. We screen for primary aldosteronism by measuring a morning blood test for aldosterone and renin. If the patient is hypertensive or hypokalemic. We screen for pheochromocytoma if the unenhanced-CT attenuation is greater than 10 HU. If it's less than 10 HU can't be a pheo, no reason to screen. Greater than 10, we should screen. I didn't mention this, but 60% of adrenal pheos operated at Mayo Clinic were discovered as adrenal incidentalomas.

So, that old presentation of presenting with paroxysms, hypertension, palpitations, headaches, sweating, tremor, pallor that's gone. We're finding most of these patients as adrenal incidentalomas. Pheochromocytomas between 1% to 2% of all adrenal incidentalomas will prove to be pheochromocytoma. If you're looking for a pheo in your clinical practice, you're wasting your time looking at your hypertensive group. You should be looking at your adrenal incidentaloma group. All patients need at least one follow-up image and of all the cases we've discussed today, the ones I'm most concerned about are those lipid-poor adrenal masses and how they should be managed in the short term and long term.

Matt: Fantastic. All right, and we will be back with our lightning round.

[music]

Matt: Tell the audience, they've heard your bio, but tell them a hobby or interest that you have outside of medicine.

William: Something I do for exercise a couple of times a week is I chop wood. That's maybe different than what most people might do for exercise.

Matt: That is a great answer. Is that kind of a meditative thing to be chopping wood? It seems like it could be.

William: It is fantastic. It's really a good workout number one, but yeah, it is a bit meditative.

I mean, you have to have wood that's going to split, so you don't want to be using elm or something, but ash and oak are great types of wood to split.

Paul: Now, are we using maul or are we, like, looking at the specific grains? How deep into this are we getting?

William: See, see, Paul knows a little bit about this. Yeah. So, I use a chopping axe. Yeah, you could use a maul, too. Sure.

Matt: That's one of my favorite answers, Paul, to that question, I have to say.

Paul: Yep, we become progressively less interesting as each year goes past, Matt. Along those lines, we like to or at least I like to ask, I've actually kind of run out of pop culture stuff to kind of dredge through. This doesn't have to be pop culture necessarily, but I wonder if you could recommend book, movie, TV show, any piece of art or literature that you've enjoyed recently that you think our listeners might enjoy as well.

William: I guess I'll give you a couple. I mean, the first one most people know about and can't remember the provider right now, but it's *Ted Lasso*, which is about soccer, but it's more about life than soccer. That's something great to watch if some listeners haven't tuned into that. With regard to reading, I have a book for you that is definitely not a bestseller. It's called *Norwegian Wood*. It's written by Lars Mytting who's from Norway, and this is the Scandinavian culture of chopping, stacking, and burning wood. You learn a lot about the Scandinavian culture in reading this book.

Paul: incredible recommendation. Excellent. I'm actually deeply interested. Thank you for that.

Malini: No, the wood comments trumps anything I would ask. That's amazing. [laughs]

Paul: This has been another episode of The Curbsiders, bringing you a little knowledge food for your brain hole.

Malini: Yummy.

Paul: [laughs] Perfect. That was the exact level, hit it out of the park. Get your show notes *@thecurbsiders.com*. While you're there, sign up for our mailing list to get our weekly show notes in your inbox plus, twice each month you'll get our Curbsiders Digest recapping the latest practice-changing articles, guidelines and news in internal medicine.

Matt: We're committed to high value practice-changing knowledge, and to do that, we need your feedback, so please subscribe, rate, and review the show on Apple Podcasts or on Spotify. You can also send an email to *askcurbsiders@gmail.com*. A reminder that this and most episodes are available through VCU Health for CME *@curbsiders.vcuhealth.org*. And I wanted to give a special thanks to the great Malini Gandhi for writing and producing this episode and to our whole team. Our technical production is done by the team at Pod Paste, Elizabeth Proto runs our social media, and of course, Stuart Brigham composed our theme music. With all that, until next time, I've been Dr. Matthew Frank Watto.

Malini: I've been Malini Gandhi.

Paul: And as always, I remain Dr. Paul Nelson Williams. Thank you and goodbye.

[music]

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