



American Society of  
**Anesthesiologists™**

Central Line

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Episode Title – Inside the Life and Research of a Physician Scientist

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(SOUNDBITE OF MUSIC)

VOICE OVER:

Welcome to ASA's Central Line, the official podcast series of the American Society of Anesthesiologists edited by Dr. Adam Striker.

DR. STRIKER, HOST:

Welcome to ASA's Central Line. I'm Dr. Adam Striker here with Dr. Max Kelz, Associate Professor in Anesthesiology and Critical Care at the Perelman School of Medicine at University of Pennsylvania. Welcome to the show Dr. Kelz.

DR. KELZ:

Thanks for having me. It's a pleasure to speak with you.

DR. STRIKER:

Well, we're excited to learn more about your research, your experiences with grants, thoughts on mentorship, all those things, and we really appreciate you taking the time to talk with us about your life as a physician scientist. One thing I wanted to start, maybe just give a brief overview of generally what you're working on now and, um, as we delve into the conversation a little more about details, and research, and grants etcetera, but just want to give a brief overview about uh, your current projects.

DR. KELZ:

Sure. So, um, ah, as you mentioned I'm a physician-scientist. I spend about 30% of my time taking care of patients in the operating rooms at the, ah, University of Pennsylvania, and 70%, ah, conducting basic and translational research. The questions that my lab is most interested in relate to where and how the brain enters and exits states of anesthetic induced unconsciousness and this interest grew from a case that I had as, ah, a first-year anesthesia resident. I had the good fortune to take care of a patient with narcolepsy and cataplexy who came in for a standard repair of a, of a femur

fracture, but that was about the only standard aspect to her case. She had a straightforward general anesthetic that was isoflurane-based but instead of regaining consciousness 10 to 15 minutes after the anesthetic was shut off, it took her more than 6 hours to regain consciousness and that got me, ah, wondering how these drugs that I was learning to use worked, and how they obtund consciousness and what the processes, ah, were by which the central nervous system came back online as it exits states of general anesthesia.

DR. STRIKER:

Well, let's pick it up there. I wanna delve into your research a little more a little later in the podcast, but as you mention, you have a, it's a, it's a really interesting story on how you got started on the physician scientist track at least correlating with your experience as a resident and can you delve into a little more detail - how you went from there to fostering a career as a physician scientist?

DR. KELZ:

Yeah, so I, I knew very early in career that I was interested in learning more about how the brain works. I wasn't sure exactly what type of research I would ultimately wind up doing, but knew that I wanted to better understand how the brain works. I thought I was going to wind up doing research into basic pain mechanisms, but in fact this case very early in career got me thinking more about the neuronal circuits upon which anesthetics act to cause a loss of consciousness as I, as I mentioned earlier. The way that I got started, that transition from residency to ah, junior faculty included following up on this observation of this narcoleptic human patient. I was in an early predecessor to the research track residency that are, that are more common these days than 20 years ago. Uh, and I used some of my clinical training time during anesthesia residency to, uh, translate and pursue this question of how narcoleptic individuals enter and exit states of general anesthesia. And so I, I began a collaboration with Masashi Yanagisawa who is at the University of Texas Southwestern and his group had genetically engineered mice with narcolepsy and cataplexy and I began studying those animals as a translational model to try and better mimic the human condition. One of the very early things that we found was that these transgenic animals that develop narcolepsy with cataplexy about two months after being born, was that they had a normal sensitivity for entering states of anesthesia, but also exhibited problems exiting the state of anesthesia. And, and this early finding pointed to the possibility that the way in which the brain enters and exits states of general anesthesia may um, may not be mirror images of each other and that, that question has been one that's fascinated me for the last two decades.

DR. STRIKER:

Well, thanks Max. I'm really excited to delve into your research, the details in just a little bit, but before we do, want to circle back to talk about the grant process and um, maybe a brief overview what it entails that because we have a lot of different listeners and potential physician scientists listening, whether students or residents. Might be interesting just to, uh, spend a few minutes covering the grant process – what it is, how it's helpful, whether it's needed or not.

DR. KELZ:

Sure, I'd be happy to answer that. So I, I consider myself very fortunate in that, as a resident, I applied for one of the, um, mentored training grants from FAER and was very lucky in that I got that grant while I was still a resident, so that that grant kicked in on July 1st the year I finished my residency training. That FAER Starter Grant gave me two years, um, in which I was guaranteed, um, 75% protected research time, uh, and I use that time to work with a couple of mentors to learn more about the endogenous regulation of sleep and arousal, and to study how anesthetics might work in this mouse model of narcolepsy, uh, to which I eluded in which that regulation of n-normal episodes of sleep and wake become deranged. The initial grant support from FAER was, uh, essential in that it showed a belief that I could take these ideas and translate them into something more. Um, and I have remained very grateful to FAER for their early career support. There are a number of grants that FAER offers to students at various levels of training, ranging from, ah, medical student research grants up through grant opportunities for, ah, residents and fellows and that includes, ah, this early career development award, the MRTG, which is a program that I and many others were fortunate enough to capitalize on.

DR. STRIKER:

And just to back up, in case some of our listeners may be early career anesthesiologists or other students aren't, they may not be as familiar, uh with FAER, can we, can you just tell our listeners what FAER is?

DR. KELZ:

Oh, yes, absolutely. So FAER is the Foundation for Anesthesia Education and Research. Their mission is to really advance the science and education of anesthesiology to ultimately empower, our ah, physician scientists, as well as to ah, come up with better ideas to help take care of the patients that we see on a daily basis.

DR. STRIKER:

Other than FAER, are there other opportunities or avenues that perspective scientists can pursue?

DR. KELZ:

Yes. Thanks, thanks for asking. Um, uh, in fact, anesthesiology as a specialty is very lucky in that the major societies have come together to try and promote the academic growth and development of our aspiring physician scientists. So in addition to FAER, the International Anesthesia Research Society or IARS also offers a series of mentored research training grants that are very similar to the mentored grants offered through FAER. I think both societies are seeking to promote the growth and development of our, of our trainees.

DR. STRIKER:

Excellent. So what advice do you have for younger physician scientists, acclimating to the grant application process?

DR. KELZ:

Sure. So the first bit of advice that I wish I had told my younger self was to start on the grant process early. It takes um, much longer to complete these grant uh, applications than you think it might. In my case, I got, uh, six months of time during my residency. I divided that pretty much equally into thirds. I spent roughly two months reading and learning more about what was known on the regulation of sleep and arousal. Uh, another two months during residency of conducting, uh, experiments and I would say a, a final two months of spending near full-time writing up, ah, this grant proposal which as I mentioned, I was very fortunate to get.

DR. STRIKER:

Let's go back into the research specifically. Am I making too much of a leap to think you're going to give us some, right here on this podcast, the mechanism of how general anesthetics work?

DR. KELZ:

(Laughter) I would love to be able to do that. With two decades of work from my lab and, uh, a decade's, uh, from others, uh, what I can tell you is that, uh we still don't completely understand how the drugs that we use every day in the ORs and procedural sedation rooms and ICUs truly work. We've learned a lot about the molecular targets

upon which anesthetic drugs act, and over the last two decades we've learned more about the neuronal targets upon which commonly used anesthetic drugs act, but the short answer is that I'd say it's still mysterious as to the exact chain of events that begin when, um, an anesthesiologist gives an anesthetic drug to a patient and culminates entry into the anesthetic state, as well as, I would point out the processes through which that state is reversed when the anesthetic drugs are either metabolized, redistributed or eliminated.

DR. STRIKER:

Well, Max, I wanted to ask. We've all learned theories about how anesthetics work. Is there a, uh, theory out there that you think has been pervasive but discounted, or proved false, or at least maybe that we think of incorrectly when it comes to the mechanism of anesthetics on the brain?

DR. KELZ:

Yeah, that's a great question. Thank you for asking. Um, you know, I can tell you that one of my early assumptions was that, um, that the process of entering and exiting states of anesthesia would be, uh, mirror images of one another or symmetric processes, and I think one of the most interesting parts of, uh, of our work with narcoleptic mice, uh, that seems echo at least a subset of patients with narcolepsy who undergo anesthesia, is that that reverse process of coming out of the anesthetic state, uh, may be partially or wholly distinct from the process by which the brain enters the anesthetic state. We had assumed that narcoleptic mice and, and, by analogy some narcoleptic human patients as well, might simply be hypersensitive to entering states of anesthesia. But since their blood pressure didn't collapse with a standard induction dose, I have hypothesized that this alleged hypersensitivity might just be something that as clinicians, we missed.

Uh, one of the big advantages to using animal models was that we were able to test this idea directly in the mouse, and surprisingly at the time we found that our narcoleptic mice showed an equal sensitivity for entering states of general anesthesia, when compared with, uh, sibling littermate controls. But, similar to this narcoleptic patient whom I took care of years ago, the mice that were genetically engineered to have this primary disorder in the organization of sleep and wakefulness, showed a specific problem exiting a state of general anesthesia. And this finding, which was supported by the observation that at the same point in time at which narcoleptic animals remained in the anesthetic state, ah, and their siblings were coming out of the anesthetic state, that at that moment in time brain concentrations of the anesthetic were equal between groups, arguing that in fact, this difference wasn't the simple pharmacokinetic change,

but rather hinted to a pharmacodynamic process that was different somehow between the narcoleptic mice and sibling controls. And what I would say more generally about our theories of how anesthetics work is that we don't yet have a complete understanding of what these differences are. If there are different molecular or neuronal processes that underlie this difference between entering and exiting states of anesthesia, but it's something that we, and others, are actively looking into.

DR. STRIKER:

Maybe a basic question, but important to ask: What is the importance of all that? We all use drugs. They seem to work. Everybody wakes up. We're all about patient safety, and for the most part, we've made this a safe specialty and, um, so what would you say to that question? Is it, is a, how is, what's the importance of knowing the molecular mechanisms?

DR. KELZ:

Yeah, thank you, thank you for asking that, and, and for pointing it out. As clinicians, we are extremely lucky in that the anesthetic drugs work extremely well. In fact you know, I'll challenge are medical students to find another class of drugs that work with a, at 99.9% of the time. So you are absolutely correct in saying that the existing anesthetics work very well for producing states of anesthesia, and most of the time our patients don't have problems exiting states anesthesia. That said, with more than 300 million general anesthetics delivered around the world every year, uh, even that small failure rate at .1% failure rate winds up leading to a potentially large number of instances in which our anesthetics don't work, as, uh, as ideally as we would like as clinicians, and so we know that the rates of awareness with recall under anesthesia are something on the order of 1 to 2 in 1,000 cases.

We also know at the other extreme, that, uh, some patients will have a delayed or protracted emergence from the anesthetic state. What we now believe happens is that the brain jumps through intermediate hops on the way from deep states of general anesthesia back up towards wakefulness. And one of the interesting questions that we have is whether some vulnerable individuals may get stuck in one of these metastable intermediate states on their way to wakefulness. We wonder if these hypothetical metastable states might represent cases in which emergence delirium arises or potentially if these metastable intermediate states are a little more consolidated and take longer to resolve, if this might not represent a, a novel framework for trying to understand some of the post-operative neurocognitive uh, dysfunction.

DR. STRIKER:

I, this certainly has ramifications throughout the perioperative process. In, in, extent even more than that, but would you say that, not only leading to potential better, more ideal anesthetics, understanding all this, but also the potential for more accurate monitoring of the, uh, the anesthetic wakeful state, do you foresee a lot of clinical applications in that regard for your average anesthesiologist down the road?

DR. KELZ:

Yes, um, so I do believe that there are applications - some within anesthesiology, some outside of anesthesiology. As you may know, it's still controversial as to whether the anesthetic state represents something more akin to coma, or something more akin to a deep state of non-REM- like sleep from which the anesthetized patient can't wake up. If we follow that analogy, I would argue that understanding more about the brain state transitions offers potential insights, uh, both into the neurobiology of sleep and arousal, as well as into pathologic states in which consciousness is impaired, um, like coma. So you can imagine if we understood the state transitions, um, or flickering between metastable states that we see with detailed laboratory investigations, we might be able to better predict in a cohort of comatose patients, individuals that have the capacity to regain consciousness. For a more practical standpoint within the realm of anesthesiology, we might be able to get better predictions as to when a patient is about to undergo a state transition safe from the unconscious state back to the conscious state either, in conjunction with the ending of the surgery and anesthetic, or perhaps in the midst of a procedure where we want to try and prevent covert awareness from, um, manifesting.

DR. STRIKER:

Well, as you talked about, the clinical practice we mentioned that, how do you think the research you've done has impacted your personal clinical practice?

DR. KELZ:

Well, um, I think as a physician scientist, uh, part of my training has included having a healthy skepticism for various bits of data that come in in the OR, so I, I find that when I receive discordant information, whether it's hemodynamic data, or say a blood gas that doesn't quite make sense based on what I expect in the OR, that I tend not to put 100% weight behind any one piece of evidence and try and, uh, reconcile the clinical scenario that fits the largest portion of the data in front of me and then try and ask what additional pieces of data might I need to get, to be more certain for events that, um, my patient is experiencing.

DR. STRIKER:

Most of the time when I peruse Journal articles, I'm not a bench scientist and I'm not doing bench research. A lot of times, I'll go straight to clinical articles or clinical trials, and I'm not sure what the right answer is necessarily, but I wanted to get your opinion on, as a clinician, is there an advantage, should we be perusing the bench research articles more in the journals? Or at least getting a feel for what's out there, or is, do you think it's something that's more akin to other physician scientists that are well within that world?

DR. KELZ:

Well, in general I would advocate, um, for all of us to read each other's literature more. You know, whether the specifics of the, an experimental design and set up feel familiar or not, I think one of the most, um, important things we can do as physicians, is to try and better understand the evidence behind various conclusions. And, and, that's true whether we're reading clinical trial literature or basic science, uh, reports. Admittedly, if you're a basic scientist trying to read the clinical literature or clinician trying to read the basic science literature, ah, the particular details can sometimes be challenging, but I'd argue that well-written manuscripts should help all readers understand what the important questions are, and the author's approach to the data to support their conclusions.

DR. STRIKER:

As someone who's engaged in that research quite a bit, do you feel that that's helped you, maybe even more so, um, in terms of critically evaluating a piece of research or an article and, uh, draw your own conclusions?

DR. KELZ:

I do. You know, what I found is that as we've tried to translate some of our studies from mice into humans, I've gained a whole new appreciation for the difficulty in conducting clinical trials and clinical research. The other thing that I've become very aware of is looking carefully at the methodology, ah, of the clinical literature and trying to make sure that the conclusions that are often cited in clinical studies actually apply to the patient to which I hope to apply those results in the operating room.

DR. STRIKER:

What do you think about academic anesthesiology in general? I just want to know you're your take is on the future of the field of study in anesthesiology; just get your general thoughts.

DR. KELZ:

Yeah, so I, thank you for the question. I, I think that anesthesiologists are amongst the brightest and most inquisitive people that I've encountered in medicine, um, certainly a group of mentors that I had as a medical student attracted me to the field of anesthesiology and helped open my eyes to many questions that had yet to be asked and answered. I would argue that within anesthesiology, we have the potential to make important observations and at, at, its core anesthesiology is a specialty that's very amenable to the scientific method, in that we can come up with hypotheses for, uh, what maybe be befalling our patients, design experiments even if we don't tell ourselves that we are testing some hypothesis, but we often will ask whether a patient is hypotensive because of being under resuscitated, will then intervene giving either fluid or blood, and ask if we've corrected the underlying deficits. So, uh, at its core I'd say anesthesiology is really, uh, an applied experimental clinical neuroscience. Now, I don't mean to scare off any potential patients that might be listening. I'd say that as a specialty we have learned how to deliver anesthetics very safely. But I'd like to emphasize the fact that at our very nature, I believe we as anesthesiologists are, um, amongst the most inquisitive cohort of physicians. And I also believe that with, with, a curious mind, ah, you never know when you're going to make an important observation that may have translational relevance.

As I mentioned earlier, I came into the field assuming I was going to do basic research in pain and yet the single experience with the narcoleptic patient who didn't regain consciousness when she should have started to make me wonder how the drugs I was using every day and, and giving to patients truly worked. And that has opened up 20 plus years of, of, questions that I'm still trying to answer. So I truly believe that, uh, if we continue to ask ourselves why and how things happen, uh, we have the potential to make a large number of important discoveries.

DR. STRIKER:

You know, you mentioned, uh, mentors. Can you take me through who you thought helped you out the most when you were first starting out?

DR. KELZ:

Ah, absolutely. So as an MD PhD student at Yale, I worked with, uh, Eric Nestler who is a psychiatrist and I studied the molecular genetics of drug addiction for my PhD thesis.

When I told Eric I was interested in pursuing anesthesiology, he put me in touch with Hugh Hemmings. I, I don't know if Hugh would remember having this conversation with me, but, uh, Hugh took about an hour out of his day back when I was a returning third-year medical student to talk to me about important questions in anesthesiology, to point out the fact that physician scientists would be welcome in anesthesiology, and, uh, really helped introduce me to the field, which to this day, I feel extremely grateful for. Throughout my residency training at Penn, I'd been fortunate to be surrounded by a number of phenomenal clinician scientist mentors, including David Eckmann, and Rod Eckenhoff. David served as my clinical preceptor and taught me something that at the time I didn't really appreciate. As a physician-scientist during residency, my mind kept jumping to questions that I wanted to pursue in the lab. David emphasized to me over my years of anesthesia residency training how important it was to focus on turning myself into the best clinician I could possibly be. And he over and over reminded me that those residency years are the only period in life in which I would have the time to focus nearly all of my efforts on becoming a phenomenal clinician. And David reminded me and reassured me that maintaining that spark of curiosity would pay off but wasn't something that I should worry about jumping back and forth between the lab and the OR, that I should really focus on, on, clinical training in those early residency years, and that's a lesson that I continue to perpetuate in our aspiring clinician scientists.

I was very fortunate to have Rod Eckenhoff, who has been my vice-chair for research for, uh, my entire tenure at Penn. Rod helped to facilitate many discoveries in my lab and pointed out many, many questions that I hadn't thought to ask that led to important discoveries over the years. I can't mention strongly enough how essential it is to be surrounded by, um, by good mentors and you can find them in a number of places.

DR. STRIKER:

Well, obviously it sound that you had some great mentors and we could all be so fortunate to have that, I, but I, I do think it's important to re-emphasize that any of us never know what kind of an impact we're going to have on student a resident, anybody who's thinking about getting involved in science in general, and taking that extra time as you said may not, you may not even remember it but the impact you could have on someone else is so profound.

DR. KELZ:

I couldn't agree with that more. Often it's the little interactions that we don't even realize we've had as mentors that can be influential, and again, I'll return my gratitude to Hugh Hemmings, who served a, a very critical role for me at a point in time that, uh, he may not even be aware of.

DR. STRIKER:

You know, as long as we're talking about your kind of up-and-coming in the, uh, field of anesthesiology and getting involved in research, what first got you involved in the idea of being a basic scientist? If you can go back, like, what first sparked your interest in that, in this field - even before anesthesiology?

DR. KELZ:

Even before anesthesiology. So, um, I had some phenomenal teachers at my public high school that turned me on to, ah, science very early on. Uh, in fact throughout my high school years, I thought I was going to go into physics either particle physics or astrophysics. I, I spent summers working at Northwestern University, uh, with one of their telescopes and doing computer programming for the gamma-ray observatory, which was a, a mission launched by NASA. It wasn't until the middle of my college years that I got very interested in questions closer to home in how the brain may work. In fact, the single experimental spark that got me excited about doing neuroscience was, um, an observation that I made as, uh, as an undergraduate working in Eric Nestler's lab, and that was the changing the expression of a single gene in the brain of a mouse could have a profound impact on its behavior. So a minor alteration in a transcription factor expressed in a reward circuit turned a normal mouse in to one that was highly susceptible to drug addiction and that idea that tweaking the expression of a single gene could lead to something is profound as altering a social behavior was one that I never forgot. And, um, I became almost single-minded about wanting to understand more about how the brain works.

DR. STRIKER:

How do you, um, advise someone that wants to get into a career as a physician scientist? What advice would you give them?

DR. KELZ:

Well, um, the first bit of advice that I give them is that anesthesiology is a wonderful discipline to pursue a physician-scientist career. We have the somewhat unique opportunity of, uh, very intense interactions with our patients. I'd argue we get to know as much about a patient's heart or lungs, kidney, liver as their traditional specialist might. At the same time, when we're not scheduled for clinical duty, ah, there are very few instances in which we get pulled back into the clinical arena, and what that means is that we have the opportunity to have very consolidated and dedicated time devoted to research, whether that's clinical research, translational research, outcomes research, or

basic science. So, I, I think anesthesiology is, is a wonderful field to pursue a clinician scientist career.

DR. STRIKER:

Well Max, this has been really informative. Before we wrap up, I'd like to know if there's anything you want our audience, or anyone out there that might be listening, to take away from our talk?

DR. KELZ:

Yeah, thanks for asking Adam. Um, what I would say is that, um, at our core, uh, anesthesiologists are applied clinician-scientists. We applied neuroscientists, really. Um, you won't find many anesthesiologists describe themselves that way, but that is very much how I feel about our specialty. We use pharmacology to modulate physiology and to help safely take care of patients and in the process, um, we have the potential to make really, ah, remarkable discoveries. We can have, uh, opportunities to gain insight into, ah, our patients' physiology, as I mentioned. I'd again highlight the importance of, of being curious in the operating room, of asking why and how. I feel like those two questions have helped me immensely with my career. Uh, in fact, um, my entire research career grew out of those simple two questions, ah, wanting to know how and why this patient that I took care of nearly 20 years ago as a resident didn't promptly exit the state of anesthesia. And so I would argue there's a wealth of opportunity in the specialty, uh, for us to make important discoveries that the beneficially impact our patients.

DR. STRIKER:

Max, thank you so much for your time. This has been a fascinating discussion. I wish you luck with your research and I look forward to seeing what you do next. Thank you so much again for spending the time with us.

DR. KELZ:

Thank you for having me on. Take care.

DR. STRIKER:

This is Adam Striker. We will see you on another episode of ASA's Central Line. Thanks for joining us. See you next time.

American Society of **Anesthesiologists**<sup>®</sup>

(OUTRO MUSIC)

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