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TRANSCRIPT - GR 10 21 22 *"The dog that didn't bark: What have we learned from asymptomatic viral respiratory infections?"* – Ronald Turner, MD from the University of Virginia

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- 00:21:47Good officially. Afternoon. Everyone um
- 00:21:52and um welcome to everyone here, and everyone joining us virtually to the forty fifth annual
- 00:22:01boom and lecture. Um! I am Meg Keeley. I am a senior associate Dean for education at the school of medicine. I'm. Also a professor of pediatrics and um, I am the very fortunate recipient of the bowman award in
- 00:22:16nineteen ninety-one, um and uh it is. I am the University trustee of the Bowman Fund, along with my colleague, Dr. Jean Mcgarran, and pediatric surgery, and every year it is our privilege to join you here at internal medicine. Grand rounds um for the bowman lecture um, and every year I have the privilege also of um speaking a little bit about Dick Bowman himself, who you see his picture there. Um! Who we honor the memory of with this award um, and in recognition, and this lecture.

Unknown Speaker

00:22:46Um,

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00:22:47so to tell you just a little bit about Dick. He was born in one thousand nine hundred and forty-five and Stanton Virginia over the mountain, and he attended hem in Sydney and Farmville majoring in American history, and he taught um for two and a half years, and then did some graduate work before he came here to medical school in one thousand nine hundred and seventy um during the clinical portion of the curriculum. So the third and fourth year he um struck many people with his good nature, his maturity, zeal, and common sense would set him a part in dealing with patients and their complex problems.

- 00:23:16He brought together the theory and the practice of medicine in a way which was exceptional for a young position at any level of training, and as a result. His clerkship performance was uniformly outstanding.

- 00:23:27During medical school Dick met Elizabeth Um while she was attending Sweet Briar College in Amherst Virginia, and they married in the spring of one thousand nine hundred and seventy-four in Greenwood, South Carolina, and then he began his Residency in Internal Medicine at the New York Hospital, Cornell Medical Center in New York City.
- 00:23:41Uh. His performance there as a clinician and teacher not surprisingly won him the universal respect of his fellow positions and students, and the loyalty of the many patients that he cared for.
- 00:23:51As uh one of his colleagues at uh New York Hospital, observed Dick, was one of the nicest persons I have ever met a joy to have around. Seldom have I met anyone who got such pleasure from life, who enjoyed his work so much, who balanced the conceptual and the practical so nicely.
- 00:24:06He seemed to embody all the best qualities that make a good physician and a happy man. He was intelligent kind, and had a keen interest in human problems. He had an unusual capacity of uncomplaining hard work, and his sense of responsibility towards those for whom he cared was never for a moment compromised by thoughts of self.
- 00:24:23Dick and Elizabeth had planned to return here to Charlottesville in one thousand nine hundred and seventy-seven to start a fellowship in infectious diseases. Uh, but unfortunately Dick died in a sailing accident. That may
- 00:24:34his family his friends, his colleagues, his teachers, turned this tragedy. Um, really into what has become the highest award uh the highest honor uh granted to any medical student at the University of Virginia.
- 00:24:46The nomination Committee, which consists of Um, all of the clerkship directors here in our Charlottesville campus, and at our Nova Campus Um Review. The performance of the entire class and nominate uh students who best embody the ideals of Dr. Bowman.
- 00:25:02Um, and I, i'll tell you that you know eighty plus students get nominated, which is just a testament to the medical students at Eva. Uh. And somehow the Nomination Committee narrows it down to five Bowman scholars who best exemplify the spirit and ideals of Dick Bowman, and those are as
- 00:25:20as as as articulated by the original founders integrity and uncompromising strength of character, and his or her personal and professional life enthusiasm for the acquisition and perfection of those skills which permit the physician to provide the best possible care for his or her patient
- 00:25:36and genuine compassion for the ill which complements a scientific approach to their unique problems, regarding them first and foremost as persons in need of help. And finally, like Dr. Beauman. The recipients should

be truly open, accessible, and approachable, with the diverse range of private interests and experiences.

- 00:25:53So every year we select five Bowman scholars. We um honor them uh at a dinner which we did last weekend uh at Alumni Hall, and many of the original founders and trustees are there, in addition to lots of the nomination committees, and over the years, you know, there have been a lot of Bowman scholars, so many of the moment scholars return for the event as well, and it was it was amazing. And um and a lot of an honor to honor our students in this way. Um! If you walk by the library You probably have.
- 00:26:23I've noticed on the outside, on the bricks there is an amorphous wood paneled uh plaque um that has lots of little brass plaques on it, and that has the names of all the Bowman scholars for the last forty-five years. And I think you will recognize a lot of the names in your department and in other departments here at Uva. So I hope you'll take a look.
- 00:26:42So it is my honor to um recognize the five Bowman scholars um, three of whom it looks like, are able to join us so far today. Um first Ashley Bolt, who um originally from San Antonio, Texas. Uh, and then uh family is now in Gaisersburg, Maryland, Uh. Ashley, Uh. Got her Bs in biology
- 00:27:00here at Uva, in addition to a passion of arts and religious studies, worked for one year at the Nih and Translational research, and then completed a Phd. Here at Uva and neuroimmunology, where she studied the Meng's after traumatic brain injury, and Ashley is um currently applying for residency in internal medicine. Um. So I'd like to recognize actually boat if she could just wave.
- 00:27:25I'd also like to honor Uh. Anthony de Novio. Anthony was born in Long Island, New York. His family now lives in Northern Virginia. He received a bachelor of science in biomedical engineering here at the University of Virginia. He was also one of our first biomedical engineering clinical scholars, for some of you remember where we embed the undergraduate Bme students with the um third-year medical students. Um, and you probably had some of them on your services. So he was one of the first, and then came to medical school here, and Tony is applying for residency, as we speak, in orthopedic surgery. So congratulations,
- 00:27:55congratulations to Tony
- 00:28:01Rohan Karant, who is from Manassas. Virginia's family, is in Northern Virginia now. He received a bachelor of science and systems engineering at the University of Virginia, and is currently applying for residency in internal medicine. So congratulations,
- 00:28:17Emily Larkin. We Don't see Um, originally from Maryland, attend to the University of Maryland College, Park Um received a bachelor of science in biochemistry, and a minor in Spanish language, um and business and

culture. She then worked in a pathology lab at the University of Maryland School of Medicine, studying pancreatic extran tissue, and is currently applying for residency in Anesthesia. So congratulations to Emily

- 00:28:42and I'd like to acknowledge Um Maggie Celesky, Uh. Maggie is from Tuscaloosa, Alabama. She um attended the University of Alabama, where we she received bachelor of science and biology and Vachel of arts in Italian um. She worked as an Americorps intern for a year um before coming to medical school, and is applying for residency in internal medicine,
- 00:29:02and all of us. Uh the five Bowman scholars are all honored on the plaque um, and we interview them all, and we choose one, as the founders originally designed to receive a scholarship, and the recipient of the scholarship this year will be Maggie Celeski Maggie. Please come up and proceed. Your scholarship one hundred and fifty

Unknown Speaker

00:29:29your congratulations.

Medicine Grand Rounds - UMA

00:29:33So again thank you all, and it is um our our enormous honor to have Dr. Ron Turner to deliver the forty fifth annual boom in lecture, and he will be introduced by your chief resident. Thank you all.

- 00:29:49Well congratulations again. Uh, to all the moment, scholars. It's very impressive. I think I'm still waiting for the day. I get more than the little trophy. I got it Soccer Camp for most enthusiastic, so very good work. Uh, So our keynote lecture today is Uh. Dr. Ron Turner.
- 00:30:06He is a specialist in the field of pediatrics and infectious disease, currently holds an appointment here at the Uva School of medicine as a professor of research, and Professor Emeritus in Pediatrics
- 00:30:18wasn't long ago, however, that he was the Associate Dean for clinical research at the School of medicine as well as the Fellowship Program Director for the Pediatrics Department.
- 00:30:28Uh Dr. Turner's research career is quite expansive,
- 00:30:31and he's had a funding from every major Federal department. You can imagine the Nih, the Ni Aid, the Cdc Uh Department of Defense Darpa. Many others. His research has focused largely on respiratory viral illnesses, and he will talk to us today about the importance of understanding asymptomatic, viral, respiratory infections.
- 00:30:52So please give a warm welcome to Dr. Rob Turner.

- 00:31:00Thanks, Sam, let me add my congratulations to the bowman's callers pleasure to be here for your for your honor. So um! The title of my talk is the dog didn't bark. What have we learned from asymptomatic, viral, respiratory infections?
- 00:31:18This came about as a result of a conversation I had with one of my colleagues and pediatrics Who was, was the moaning uh the number of asymptomatic infections that were being detected as part of all the surveillance that's been done Uh recently around Covid.
- 00:31:36Uh. And he was quite surprised not an infectious disease person, but he was quite surprised at how many asymptomatic infections there were, and I suggested to him that this wasn't new, that this was something that we've known for uh for quite a while, so we'll. We'll explore this a little bit
- 00:31:52uh, I do have some um uh industry involvement, none of which is is relevant, I don't think, to uh to the talk today.
- 00:32:03So the occurrence of asymptomatic infections. As I say, this is not a a new phenomenon. It's been around for a while. One of the best examples of this is in this paper from two thousand and fifteen, where they essentially took a one hundred and eight individuals, members of twenty-six different families, and this was done in Salt Lake city.
- 00:32:26Uh, and they did weekly Pcr on these individuals with a multiplex Pcr. Regardless of symptom. Just every week they did a Pcr. On every member of these families,
- 00:32:41and what you can see is that there were a lot of infections. So Ronavirus, which of course, is one of the more important viruses. Um uh! Was very prominent. So in a one hundred and eight subjects over a one year period there were four hundred and sixteen Ronavirus infection.
- 00:32:58The interesting thing, of course, is that forty four percent of these were asymptomatic. So no symptoms to suggest any illness. Uh, and you know we're a systematic.
- 00:33:09The other thing you'll notice is that this is consistently true, regardless really a virus. There's the numbers obviously uh get small for some of these. But the um almost all of these different viral pathogens are associated to some extent with asymptomatic,
- 00:33:27uh with asymptomatic infections. So this is a this is not a new phenomenon. It's been around uh and uh, we've known about one hundred and fifty.
- 00:33:37So we're going to talk primarily today about Ronavirus for a couple of reasons. One. It's the one thing I know something about. Uh and secondly, uh, as you can see, a awful lot of these infections uh occur in in the community. The other thing that makes it attractive to talk about is that we have an experimental challenge model

- 00:33:56uh for Ron of ours. It's been used at the University of Virginia since the late nineteen sixties. Uh it was. It was uh brought here by Bill Jordan from uh Cleveland Uh, subsequently uh, Jack Walton, who was a member of your department for many years uh use. This model Fred Hayden has used the model. I've used the model,
- 00:34:17so we'll we'll use that model to explore uh this issue.
- 00:34:22So in this model, and i'm not going to describe the model in detail, there are questions about it. Please ask. But um. In this model we basically infect
- 00:34:31volunteers, healthy volunteers who are zero negative to the virus. Uh with with a ride of ours. And it's an I and d a virus has, an I d it's approved for use in humans uh for this reason,
- 00:34:46and uh oops Sorry.
- 00:34:50And um
- 00:34:53in this model we define the volunteers as infected. If on any of the five days after virus challenge, they shed virus, or if they, Sara, convert to the to the, to the to the challenge bar so pretty pretty straightforward definition of an infection.
- 00:35:09And then we evaluate symptoms severity uh using us standardized symptoms scoring that it's been used actually. Jack uh Gordon. He started using it in the early nineteen seventies, and we've used it almost without modification
- 00:35:24uh every since then, and that we so we do. A total symptoms score over the five days post challenge, and when we define a symptomatic illness by standard criteria of a symptom score greater than five for the subjective impression of a cold illness uh or three days of ron Ria.
- 00:35:43The reason we have this definition is that If you just look at total symptoms. Scores! This is the way they look in the challenge model.
- 00:35:51So this is a one hundred and ninety-three infected volunteers all of these volunteers will proven to be infected by the criteria I described earlier, and you can see there's really no breakpoint for symptomatic versus asymptomatic in this in this data set, I mean,
- 00:36:08uh, they're kind of spread out all the way along here. These two out here. Were a couple of students that we're trying to get an excuse to get out of uh their final exam. But uh, but uh, you can see they're pretty well uh spread out.
- 00:36:22Notice that the Median score was about fourteen. This is the inner quarter up tile range, and then the problem with this is this is the symptom: Scores and uninfected volunteers,
- 00:36:34so it's not quite the same. The meeting score here is five in a quartile range is is different. They're also kind of spread out. It turns out that if

you drop a virus in somebody's nose and then ask them for the next five days. If they're sick, they say yes, uh, and So you get you get a symptom score like this.

- 00:36:52So as a result of that, we ended up coming back to the, to the common cold illness definition, the Jackson
- 00:36:59criteria. And and you can see when you apply these criteria in in our data set we ended up with one hundred and twenty-four who met the illness criteria.
- 00:37:09Interestingly, thirty-six percent are about the same as what you see in the natural setting were defined as asymptomatic, and of the ones who were only infected. Nobody met the illness criteria.
- 00:37:22So the story I'm going to lay out for you here today starts with the first thing I was assigned to do by Jack uh Waltney and my fellowship. Uh, I was told that I needed to count the do a differential count on the cells, and not
- 00:37:41uh coming out of individuals with Ronavirus common colds. This was this was when I realized that, being an infectious disease fellow was really not going to be very glamorous. Uh, and so this was was my assignment, and the idea here was is that we were trying to see if there was damage to today's left. And so we said, You know, if we
- 00:38:00can see a bunch of affiliated epithelial cells in in the nasal secretions during the cold, that'll be evidence that there's some sort of damage going on in the in in the in the nasal lining. Well, as we did the the analysis, the thing that actually popped out to us unexpectedly
- 00:38:18was Poly's So you what they started with about half the sell sixty-three percent of the sales being poly before challenge, and then the number of poly and the nasal secretions increased. Uh in state uh fairly constant over the over the uh next uh, five days after challenge
- 00:38:39that was unexpected. We didn't know exactly what to make of it. But Owen Henley, Uh. Who worked with Jack uh came back a few years later and did a a a a study, where they looked at poly and nasal secretions
- 00:38:55from a defected ill infected, not ill, and sham challenge volunteers. So here's the symptoms scores, and you can see it follows a fairly typical pattern here for for total symptoms in the ill volunteers,
- 00:39:08the shams and the and the not infected uh, or the infected. Not Ill kind of bump along here with not very much in the way of symptom scores. And then this is the poly counts, and what you can see is, is the Polys go up and come down, but they only go up and come down in the symptomatic volunteers

- 00:39:27uh so infected volunteers who don't develop symptoms. They're down here uh, and so so the poly seemed corally uh with, with with the presence of of illness.
- 00:39:41Well, about this time uh th, there was a fair amount of research into into the cytokines and team of kinds, and I late had been discovered uh early in the nineteen nineties and Oops. I did it again
- 00:39:57early in the nineteen nineties, and so in in one thousand nine hundred and ninety-eight. We published this paper where we did sham challenge volunteers, and when we compared those to Ronavirus, infected asymptomatic or run of ours, infected symptomatic volunteers and looked at the concentration of Ile,
- 00:40:17which is a poly chemo tract. It's a team of kind in in in nasal creations, and what you can see is that consistent with the observations of poly's. Ila goes up in symptomatic volunteers.
- 00:40:35Subsequently we've been able to show that there's a modest correlation uh between the change in isolate concentration. So if you look at isolate on day zero prior to challenge,
- 00:40:47you, look again on day three, which is kind of the peak of symptoms. Uh, and you look at the change compared to total symptoms, for there's a a modest uh correlation here.
- 00:40:59The other thing we noticed was that that um. The one of the things that seemed to correlate with the development of symptoms was the presence of isolate or the concentration of ile and nasal secretions on day zero prior to challenge. So these volunteers are not yet seeing the virus. Uh um. But on day zero the the concentration of isolate in the in the volunteers who became ill
- 00:41:27was lower than the concentration of of isolate and the volunteers who did not become ill.
- 00:41:34So there was a a a an effect of the day. Zero isolate on these, and you could see this here in a little different way. Here's the day zero a values, and it's not a not a big difference, but it's statistically significant.
- 00:41:49Uh in in in the ones who uh were not ill. And then the thing that happens here is, they start higher, but the rise is less so. They start hired. They don't go up as fast uh in contrast to the ones who uh who become ill.
- 00:42:05So the question then, uh is, whether whether this
- 00:42:11they zero difference, can be manipulated. Is there a way to to
- 00:42:17do that? Or is this just an inherent feature of the individual volunteers? That that uh, we can't really control?
- 00:42:26Well, it turns out that there's a a molecule called poly, I see. Uh, which is a synthetic uh viral mmetic. Uh so it's. It looks like viral Rna to the to the innate immune system, but no proteins are produced. It doesn't replicate.

- 00:42:44It does activate the innate immune system via tlr, three primarily. And uh, it turns out that there is in a nasal powder form of this available that that you can use to spray into somebody's nose
- 00:43:00when you do that, what you see is what you might expect, which is, if you do placebo
- 00:43:07day two. This is prior uh to any dosing. This is five to seven hours after the first toes, twenty-four hours after the first toes, and then there's another dose given at twenty-four hours, and then five to seven hours later, and twenty-four hours later
- 00:43:24in the Placebo group. Not much happens, as you would expect. The numbers are small. This was pilot data. Uh, and but if you look in the Poly Ic group
- 00:43:35there's a somewhat of an increase after five to seven hours. It's, certainly by twenty-four hours after dosing poly I see into somebody's nose. You see in her new interlucinate uh come up.
- 00:43:48So then, if you do the study. So this was a clinical trial was actually done in the Uk. Um, and what they did here was they gave two doses of poly, I see.
- 00:44:00Uh. Then they gave
- 00:44:02right of our sixteen challenge. So in in the in the challenge model, and then they followed the volunteers,
- 00:44:10and the result of this is as follows: So in the in the Placebo group the blue line. Here they got a symptom profile that looks for all the world like any other symptom profile. And in the part of our challenge model,
- 00:44:23and in the ones who had been treated with the poly. I see it that was significantly blended. So it did appear that you could manipulate that that initial I late concentration
- 00:44:36uh, and and have an effect here. This is just different ways of looking at at this, all of which are consistent with it. An effect on on the uh symptoms. For,
- 00:44:47importantly, this was not an effect on infection.
- 00:44:50Everybody challenged with virus in this study got infected.
- 00:44:54Uh. So, in spite of the fact that they were infected. They didn't get symptoms. There was a little bit of an effect here on viral load. Remember that the administration of the drug was out here at minus two and minus one. But, uh, soon after virus challenge, the um uh viral loads were identical.
- 00:45:16So this this information suggests that nasal, inflammatory tone is associated with sympathy, so recognize that your innate immune system is not either on or off
- 00:45:28your innate immune system has a tone. You can think of it like muscle tone. You know you either straining or you're not straining, but you're

never totally relaxed. Uh, and so and so it's the same as true with the innate immune system. And so there is a tone that's associated with symptoms.

- 00:45:46Inflammatory response correlates with the occurrence of illness and the severity of symptoms in this baseline uh inflammatory state can be manipulated to alter the alter. How you respond uh to a virus.
- 00:46:01So about this time the uh, there was an awful lot of interest in microbiome. It's the techniques for doing microbiome and the techniques for analyzing
- 00:46:12uh, uh, uh, microbiome data, or or being much more widely available. And so people, my microbiome was had been studied uh for over and over again, primarily in animal models, showing that there are effects of the people microbiome on immune modulation.
- 00:46:32And so the question arose for us: was this: The nasal microbiome affects symptom uh production.
- 00:46:41So this was a study that was done. It was a probiotic study, so I'll just say from the front end. The probiotic had no effect on anything. Didn't alter um microbiome didn't alter side of kinds didn't alter Ryan virus infection.
- 00:46:56Uh, But this was the study that was done. But what we did here is you can see that we did nasal lava just on day minus twenty, eight prior to the challenge, and then For five days after challenge
- 00:47:07we collected nasal levage. Uh, Throughout the study we collected uh fecal samples for fecal microbiome uh at three different time points,
- 00:47:17and Then we measured the interluke at eight levels, and then as wash the tighters and the there's a wash, and we analyze nasal microbiome from nasal swab specimens. So uh to see what was going on uh in in the nose.
- 00:47:33And this uh essentially is a summary overview of what happened with uh, the nasal microbiome, and what you can see here and in the details Aren't. Really all that important. Each of the colors here represents a different
- 00:47:49uh genus. Uh. But what you can see here is that in spite of this, is baseline, of course, day minus twenty, eight, And then, in spite of given a probiotic in spite of given a viral infection.
- 00:48:01This really didn't change very much. I mean, there are some minor differences here, but in in the big picture. This was a fairly stable, nasal microbiome, regardless of the fact that these volunteers had um
- 00:48:15and borrow infection.
- 00:48:17One of the things that was of interest is that when you looked at it with a principal kind of components analysis, there tended to be clustering of these uh groups in the in the in the microbial. So the red here,
- 00:48:31uh represents a group of volunteers who had staff a caucus as the predominant organism in their nasal microbial.

- 00:48:39The green is a group that had griny bacterium, ally, caucus. There were some other minor groups here, but I'm not going to spend much time on them as the sample size was very small. But so these two major groups kind of fell out, and that you can see in this slide
- 00:48:55uh kind of how this looks. So this this is the placebo and probiotic uh at different time points uh day minus twenty, eight to day five here uh in the staff predominant group, and you could see that the red, the red bars represent the staff.
- 00:49:13It's it's obviously predominant. It's obviously unchanged. Really over the course of the of the illness in the course of the of the probiotic um, and so these are volunteers that have this as a baseline. This is This is the way their microphone works.
- 00:49:32Similarly, in the in the corrine bacterium Alli Pakist group, the these green bars uh lumped together here represent that. And again you can see that there's really not much change. Uh, over the course of of the illness.
- 00:49:47One of the things that fell out of This, however, was this: There was a difference in total symptoms. Score uh in the ones in the volunteers who had predominant staff, the cockle microbiome, versus those who had predominant ally, a caucus uh for any bacteria in that, and you could see that here,
- 00:50:07and it's also true here. This is the number who met the illness definition for come cold. So they remember. These are all normal, healthy volunteers, brought in, all treated exactly the same, all given uh the same virus. Eighty One percent of them developed a cold
- 00:50:24if they had staff with Caucasus, the predominant Uh microbiome uh genus and sixty-three percent with Coronavirus So then we said, Aha! So now let's look at the ile, because what we would expect
- 00:50:41is that in these who have staff with caucus, and are more likely to get ill. They should have a lower aisle weighted baseline uh given what we had already seen uh in in the other study.
- 00:50:53Well, things don't nice work out the way you think they're going to um. And so this is I. Eight uh in in Nes lovage uh staff of cockle uh these numbers. These differences aren't significant, but the staff with caucus, if anything, is higher
- 00:51:09uh than it was in the corridor, bacterium, ally, caucus uh group. So we kind of hit a dead end here. We've got this. This did not confirm our hypothesis. We now have two different things that seem to be associated with symptoms
- 00:51:26that Don't correlate uh well with each other.
- 00:51:30So we started looking around uh, and we had been involved in some other studies uh looking at other potential mechanisms for uh symptoms

severity. And one of the things that's been around for a while is psychological stress. So this is a study that was published in the New England Journal back in the early nineties.

- 00:51:49Uh. It's based on data that we're generated in the common cold unit in the Uk uh over many, many years,
- 00:51:57and they publish this uh,
- 00:52:01basically retrospective study or a retrospective look at these data looking at a psychological stress index that they made up. They said, You know what are the what are the potential stressors? And then how many subjects got cold. And so this got a lot of attention, as you might imagine. Cnn: and all that stuff. Uh with psychological stress being associated with cold, it's really a pretty crummy study the psychological Stress index is,
- 00:52:31it's very broad, includes all different kinds of things. Uh, and whether it really uh matters or not,
- 00:52:38I think a little more compelling is this study, And this is a study that Jack Waltman was involved in, where they actually broke out these stressors by different uh different types of stress. And so life events uh either negative or positive life. Events affect
- 00:52:58and uh, perceive stress, and then and then they challenge they. They did these psychological screens, and then they challenge the volunteers with virus and said, Okay, did you get sick or not?
- 00:53:08And what you can see here is this is this is uh a total symptom, or this is, uh no cold versus cold. The number who had each and the asteris here represents a P. Less than zero point zero five. So uh statistically significant.
- 00:53:26And you can see the total life, events, positive life events we're associated with increased numbers of colds in these volunteers uh affect perceived stress. So I'm stressed because I have to take an exam tomorrow that doesn't count uh that. So there. There did seem to be something here that might
- 00:53:48um might have some effect.
- 00:53:51So shelving Cohen, who is an investigator uh at at uh Carnegie Mellon University spent twenty years looking at this issue, psychological stress and and cold, and one of the things he found that I think is really quite interesting
- 00:54:08is that that he looked at childhood stress, social and economic status as a as a surrogate for childhood stress number of years of home ownership was way. He defined
- 00:54:24child with socio-economic status. And so, if if your parents own their home

- 00:54:29less than six years or seven to thirteen years for fourteen years, and These volunteers were obviously all adults at this point. Uh, there was a correlation between
- 00:54:42the number of years that your parents own their home, and whether you got ill when you got a virus dropped in your nose.
- 00:54:48Uh Now, my first reaction to this is
- 00:54:52this is crazy uh a and that's always. That's my first reaction to a lot of research. But, uh, to this in particular, say, this is really nuts.
- 00:55:02I have to say that that it gains a little bit more currency
- 00:55:07If you um
- 00:55:09recognize that we even here at the University of Virginia we have investigators who have followed cohorts for thirty years uh in Charlottesville, and they are showing correlations between childhood, stress and adult
- 00:55:23high blood pressure, adult heart disease uh that sort of thing. And so the fact. The concept that there may be childhood stressors. That then translate into adult illness is certainly not uh, certainly not crazy.
- 00:55:38So then the question comes, what, what does all this mean? How can How can you make any sense out of this?
- 00:55:44Well, so the hypothesized association between chronic stress and illness during Ronavirus infection. The first thing is that
- 00:55:53chronic stress is associated with elevated levels of circulating cortic steroids. No big surprise. So if you measure blood levels of cortical steroids or survival levels of cortical steroids. They're hiring in people who meet these definitions of chronic stress.
- 00:56:10It's also been shown primarily by Sheldon uh in this paper here that this um that the
- 00:56:19increase in circulating corticosteroids results in a down regulation of Google cocorticoid receptors. So the receptors, after a while. Say, hey, wait a minute. You know we're getting bombarded here by by steroids. We need to tant this down a little bit,
- 00:56:36and then that decreased uh sensitivity or Google Coreoid resistance results in loss of regularization, r or regulation of the inflammatory side of kind. So the glucose quarter card receptors are are involved in the in the regulation of inflammatory responses,
- 00:56:55and that this unregulated information and results in increased symptoms. And so and, like I say, there are supportive data for this. So they have been generated by Sheldon Cohen.
- 00:57:10Interesting. So then, the question is, are the cortical steroid receptors.
- 00:57:14The the link between the association with staff, a cockle Nazis uh carriage and symptoms severe.

- 00:57:22So the glucocorticoid receptors are known modulators of a native immune responses. As I said,
- 00:57:29Yeah, for us nasal carriage, it turns out, is associated with glucocorticoid gene, receptor, polymorphic. So there are four hapla types uh of the glucose quarter cord receptors. One of those hapla types is associated with carriage of staff in your nose.
- 00:57:46Now, all of you know that if you go out and you start culture, and those about thirty percent of people will have staff in their nose all the time. Chronic carriers of staff, and as far as I know, it's never been entirely clear what it is about those individuals that uh, that does that.
- 00:58:03But uh, one possibility is that it's got something to do with the hapla type of the glucocorticoid gene receptor.
- 00:58:12The other thing that's interesting about this is that these haplotides of these polymorphisms are associated with alterations and receptor sensitivity.
- 00:58:22So haplotype, one may have higher reaction reactivity to Google corticoids to less that sort of thing. So there are variations in receptor sensitivity based on uh
- 00:58:38Google quarter cord polymorphisms. So it's an interesting hypothesis uh, and it's testable hypothesis, not by me, but by some young person here really is interested in this. Uh, that? Um!
- 00:58:53What really results in the microbiome changes that we saw
- 00:58:58is not that there's anything specific about the staff aureus that we identified as part of the microbiomeic study,
- 00:59:06but that uh it's really that the half the type of the glucose quarter cord receptor in those volunteers. Uh is amenable to Staph Aureus colonization, and at the same time is also affecting the root way people react uh to the symptoms.
- 00:59:24So what do we learn, uh, first of all, symptoms and coronavirus infections are mediated by nasal and eight immune responses. I've talked about R. Of ours here. Today. It turns out this is true for the other respiratory viruses as well. Uh, primarily Rsv. And Coronavirus, which are not
- 00:59:42terribly destructive to the nasal Mucosa Um are are our mediated largely by innate responses. Uh influenza is more destructive to the mucos that may have, it may be, more of a direct viral effect or influenza.
- 00:59:57These inflammatory responses can be altered by the state of the inflammatory tone at the time of uh infection,
- 01:00:05and that both chronic and apparently in aulnerable characteristics also. In fact, these symptom responses. So you can modify the state of the inflammatory response in your nose. But there are these other chronic uh things that uh, uh seem to have effect

- 01:00:22microbiome uh glucocort, great receptor Ha! The type, and then uh chronic stress.
- 01:00:30Now I haven't talked about other possible things. First of all, interleukin eight is probably not the only side of kind uh it's involved. Uh interlucinate um is the only one that we've detected That has the correlation between
- 01:00:47rise and interlucinate, and uh symptom uh production. Um! The other thing is that genetics clearly uh, could have an effect on this. There are no uh real genetic defects, if you will, that are associated with
- 01:01:06rhino virus infection, common cold illness
- 01:01:09that are clear and predominant, that there may be subtle uh effects that we don't know about. Uh. So there are other. There are other possible explanations and what we've shown, but I think clearly uh symptom response in in these individuals. Uh is affected, and can and can be altered uh with with intervention. If if we want.
- 01:01:33Thank you,
- 01:01:42i'm happy to entertain questions.
- 01:01:54I'll start off with some questions. Then. I might as if any questions come to the chat on,
- 01:02:00so I’m going to ask you to hypothesize something here. Um, I'm good at that. Okay, that's what I figured. So you know the connections. I see kind of running through the course of this talk. Um, I’m thinking about severe asthma.
- 01:02:14There's a lot of research about how rhinovirus affects other lower airways, and there's a lot of research connecting um
- 01:02:22early childhood, maybe early childhood trauma or high childhood stress. And then that being associated with more chronic, severe, persistent asthma,
- 01:02:33do you see a common thread line here from a mechanistic standpoint
- 01:02:38that you we could make sense of. Well, so obviously as was an inflammatory process. Uh, and the hypothesis actually promoted uh here by Peter Amen. In the department of Pediatrics is that that an asthma exacerbation is actually a double inflammatory hit.
- 01:02:59You have an initial allergic kit, and then you have a viral infection that gives you a secondary uh viral uh inflammatory hit, and the combination of the two is what produces
- 01:03:12A. And as an exaceration so clearly there may be interaction, and whether the childhood effects on asthma are mediated through
- 01:03:24changes in inflammatory processes,

- 01:03:27or whether they are even in the in the um uh Ryder virus infections is not entirely clear, but certainly it's possible,
- 01:03:39having said that I think it's important to recognize, and we always talk about. I mean, whenever you write a grant for Ryan of ours you always put in there how you're going to prevent asthma, because Ryan versus the predominant cause, as you have to put, that has to be part of the this, the argument. But when you look at it all less than less than five percent of all run of ours. Infections in asthmatics result in an asthma exacerbation.
- 01:04:05I mean, you see the number of of asthma infections that occur, and if every asthmatic
- 01:04:11squeezed every time they got to run averse infection, it, it would be constant
- 01:04:16uh and it. But when you look at it, and it it depends a little bit on how you define an as exacerbation. There's loss of control there. You know all these sorts of things, but it's a small fraction of all Rhona virus infections that result in an asthma exacerbation. So there clearly has to be other
- 01:04:35factors that play uh beyond just the mere presence of the virus.

Unknown Speaker

01:04:42Thank you.

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01:04:56So all the effect that's happening with

- 01:05:04Yeah. So So we had the benefit of having two different rhinoviruses that we could use for our challenge studies. Um, we didn't we didn't do any rsv challenges. Fred, of course, did some flu challenges, um, but
- 01:05:22it with the with the two Ronaviruses. One of the things that would happen is we would have, and it was primary university students who were participating in our studies. So we had a We had four years to get a shot at them basically while they were here to uh to do their other work. Um! And what what frequently happened is we would get repeat
- 01:05:42volunteers who would come in, and they'd say, Well, I want to do this. We were paying them uh, and and they said, I want to do this because I did this the last time I Arian, got sick
- 01:05:53and we would say, Okay, come on in, and
- 01:05:57it was fairly random, but many of them went ahead and got standard ron of ours common colds uh with the second challenge. So it wasn't that you had a group that was resistant, and a group that was susceptible. I think the difference is um

- 01:06:15uh that the state of the nose varies the inflammatory state of the nose varies If you drive to work, and you're driving behind a Diesel truck
- 01:06:24uh all the way into work and inhaling nitrous oxide and self sulfur dioxide. Your nose may be an inflammatory state. Um that increases the iolate constant, or the inflammatory tone. It reduces your risk of having a symptomatic uh illness. And so the the other other evidence for that, and I didn't show it uh today, in the interest of time
- 01:06:49there there is a study that was done in San Francisco, where they gave allergic individuals an artificial allergen challenge, so that so they took individuals who were
- 01:07:02all had allergic crinitis. They gave them their allergen, produced a symptomatic allergic disease, and then challenged them with Rhona virus, and what they saw was in group in groups where they didn't give the allergen, or where they gave a placebo allergen
- 01:07:18and didn't get that allergic inflammation, and this may go back, Sam, to your question a little bit. Uh if you get that allergic inflammation, you blunt the isolate response
- 01:07:30to the virus, just as you would expect. Uh, and you reduce the reduce the symptoms uh to the virus. So I think, I think that the inflammatory tone is not fixed. I think it is
- 01:07:43variable depending on environment depending on what's going on uh, and various exposures the other, The other example may well be uh the you know the whole issue of viral interference. Uh, that's been around forever. If you've got one virus, you don't get you don't get a second virus.
- 01:08:01It's not, probably not true. But it's been around forever. But one of the possibilities is that if you're exposed to a virus while you have inflammation
- 01:08:12from the first infection that they maybe you don't get symptoms from the second infection. Um, And that may help explain the viral interference to number.
- 01:08:27Okay, thank you very much

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01:08:41This meeting that we appreciate it. Thank you.