

"Life's Little Questions"  
– SHOW 1105

Tease  
A Ticklish Question  
Laughing Matters  
Cold Comfort  
Why are Peppers Hot?  
Grains of Inspiration

TEASE

ALAN ALDA I'm about to be tickled by a tickling machine. The question is, will I laugh? Stay tuned.

ALAN ALDA (NARRATION) And speaking of laughter -- where does it come from? We give people colds... RED HAT Definitely have the cold. The cold, I have it.

ALAN ALDA (NARRATION) Then try to cure them. And we ask, why are peppers hot?

DAVE DEWITT Now you said you liked hot peppers.

ALAN ALDA Yes I do. I'm Alan Alda. Join me and my laugh box... as Scientific American Frontiers asks more of Life's Little Questions.

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A TICKLISH QUESTION

LITTLE GIRL Why do trees die?

ALAN ALDA Why do trees die? That's a really good question.

ALAN ALDA (NARRATION) I'm visiting a nursery school...

ALAN ALDA Olivia, what's your question?

ALAN ALDA (NARRATION) To find out what's puzzling the preschool generation.

OLIVIA Why are buttons round and not square?

ALAN ALDA Why are buttons round and not square? That's a great question. Kids ask the greatest questions. Why don't all the seas run down to the bottom of the world? Why doesn't my dog talk? What's that little dangly thing at the back of my throat? How can Barney be on two TVs at once? As we get older, we either figure out the answers or -- more often -- simply stop asking the questions. That is unless you're a scientist -- and then a lot of those puzzling little questions we ask when we are young keep nagging away at your mind. In this show, we meet some of those scientists who go on worrying at life's little questions -- often coming up with some surprising answers. We're starting here, on the campus of the University of California in San Diego, with just the sort of question kids love to ask. How come you can't tickle yourself?

LITTLE BOY Excuse me. I can tickle myself.

ALAN ALDA You can tickle yourself? Let's see. Can you do it?

CHRISTINE HARRIS And if you'll go ahead and have a seat right here...

ALAN ALDA (NARRATION) Despite her being a grown up, Christine Harris still wonders why we can't tickle ourselves. And she's devised, I'm told, an ingenious experiment to help find the answer.

CHRISTINE HARRIS If you agree to participate, you'll tickled twice, once by me and once by my machine. Both times you'll be tickled on the bottom of your foot. I'm going to ask you to wear a blindfold and earplugs while we do this, and the reason for that is so that you can attend to the sensation of tickle without distraction. So I'm going to strap your foot in to keep it roughly in the vicinity of the machine.

ALAN ALDA (NARRATION) Now, I have my suspicions that all is not quite as it seems here. But before I get a chance to check out the tickling machine any further...

CHRISTINE HARRIS Does that feel snug so it's not going to fall off?

ALAN ALDA It could be a little snuggier.

CHRISTINE HARRIS So the first time I'm going to have my machine tickle you. So I'll press the button, it will take a few seconds to initiate, and then it will turn itself off.

ALAN ALDA (Laughs) That was a machine?

CHRISTINE HARRIS That was the machine.

ALAN ALDA How much does that cost?

CHRISTINE HARRIS We'll tell you later. OK, on a scale of zero to seven, how ticklish would you rate that, with zero not at all ticklish?

ALAN ALDA Well, it must be seven.

CHRISTINE HARRIS OK, extremely ticklish. Now this time I'm going to tickle you, and again I'll ask you to rate it afterwards. How ticklish would you rate that?

ALAN ALDA Only around 5.5 to six. I'm sorry to say. I mean, you know, you're a nice person...

CHRISTINE HARRIS OK, OK, I'm going to go ahead and take off your blindfold now. And you can go ahead and take out your earplugs. So did you notice any difference between the sensation when I was tickling versus when my machine was tickling?

ALAN ALDA Yeah, yeah, I noticed a big difference.

CHRISTINE HARRIS In what way?

ALAN ALDA The machine was more aggressive. And relentless -- assuming it was the machine, I was blindfolded, I couldn't tell. It was as if it was reaching inside my foot, it wouldn't quit. And the second one was more courteous.

CHRISTINE HARRIS OK, OK. Would you like to see the machine work now?

ALAN ALDA OK.

CHRISTINE HARRIS So basically I hit that, it takes a couple of seconds.

ALAN ALDA (Laughs) You know that alone is worth the price of admission, just to see that. Hello. How are you? Nice to meet you. Well now, tell me about this machine. It's a complete fraud, right?

CHRISTINE HARRIS Yeah, we call it a mock tickle machine. Mock sounds better than fraud. And it just is a bunch of lights and old time sensitivity things that we thought might look like a real tickle machine.

ALAN ALDA Does anyone ever say, that's a tickle machine? What do you mean, you know?

CHRISTINE HARRIS Only one person figured out that it was not a real tickle machine. What happened is that the research assistant was under the table and she had her hair up in a pin and it got caught in the top of the table, so there was actually this noise as she tried to free herself from under the table.

ALAN ALDA So what did you find out from this test?

CHRISTINE HARRIS Well basically what we were looking at is -- no one really knows why you can't tickle yourself, right? But one hypothesis is that it requires the belief that it's somebody else doing the tickling. And if that's the case, and you put someone in here with a machine and you tickle them with a machine, then they shouldn't laugh and smile. That's what we were interested in.

ALAN ALDA Well it sounds like I completely reversed what you expected.

CHRISTINE HARRIS No, well actually you I think you fit what I would expect. That's one hypothesis. And what I think is, people who believe that tickling is something akin to a reflex or fixed action pattern, they would suggest that it shouldn't matter if it's a machine or a human, that you should laugh and smile regardless of your beliefs. And so I think this does support that kind of thought.

ALAN ALDA (NARRATION) The idea that a machine can tickle as well as a person certainly goes against most people's expectations. But in fact most of the subjects actually experiencing Christine's mock tickle machine were as tickled as I was -- if perhaps not quite as astonished. Still, the experiment has what seems to me an obvious problem.

ALAN ALDA You haven't really tested for a machine tickling a person, you've tested only for whether a person believes a machine is tickling them. If they believe that, will they have a tickle response? Have you ever had something like a machine to tickle them with?

CHRISTINE HARRIS No we haven't because for us we wanted to test this assumption that there's something about these beliefs, and for us this was the right experiment. Because if you had a tickling machine, a true tickling machine, and you had it tickling the person, and then you had a human tickling the person and you got a difference, maybe the machine didn't cause laughter and smiling as much, you would never know if it was because the tactile stimulation was different or if it was the belief in the machine. So for us it was the right experiment. But we haven't actually built a real machine.

ALAN ALDA Actually it's probably extremely difficult to build a tickling machine.

ALAN ALDA (NARRATION) Difficult -- but not, it turns out, impossible. In London, psychologist Sarah Blakemore recently built a robot that would tickle people's palms. It doesn't look as much fun as Christine's mock machine, but like hers it did succeed in being tickly.

SARAH BLAKEMORE So could you tell me how that stimulus felt, on a scale from zero meaning not at all to ten meaning extremely tickly?

SUBJECT About six.

ALAN ALDA (NARRATION) What was clever about this experiment was that subjects could also control the robot themselves. And when they did, it stopped feeling tickly -- unless the robot had a built in delay, when the tickling sensation returned. So you can tickle yourself -- but only indirectly. SARAH BLAKEMORE So you can feel the tactile stimulus on your hand now...

ALAN ALDA (NARRATION) Sarah Blakemore then put volunteers into a scanning machine to see if there was any difference in how the brain responds to self-tickling as compared to machine tickling. The experiment suggests that the brain has a self-censor, a damping signal sent from the region monitoring movement to the region reacting to touch -- a useful survival mechanism making sure we don't jump in surprise every time we touch our own bodies. So that's why we can't tickle ourselves -- our brains won't let us. But there's another little question about tickling. How come it makes us laugh? Is it because we find it funny -- funny in the same sense we find humor funny? No less an authority that Charles Darwin suggested a link between ticklish laughter and humorous laughter -- so Christine Harris set up another experiment.

VIDEOTAPE We will work with the customer to give that customer the change he or she needs.

ALAN ALDA (NARRATION) Her idea was to exploit what comics call the warm-up effect: it takes a joke or two to get the audience in the right mood.

VIDEOTAPE If you come to us with a hundred dollar bill, we're not going to give you two thousand nickels, unless that meets your particular change needs.

ALAN ALDA (NARRATION) If ticklish laughter and humorous laughter are the same, then warming someone up with a funny video should also make them more ticklish.

VIDEOTAPE We will give you the change equal to the amount of money you want change for.

ALAN ALDA So at what point do you tickle her?

CHRISTINE HARRIS So after she's watched the video, and laughed and smiled at the video, then we'll do the tickling and so Noriko... We're going to tickle you anywhere from the underarms to the waist, and so if you just loosen your arms, you can lean back but just let your arms fall kind of loose. OK?

ALAN ALDA (NARRATION) Margaret certainly didn't seem very amused.

MARGARET I'd say that was about a two.

CHRISTINE HARRIS OK

ALAN ALDA First of all, do you find that people are warmed up by watching the video?

CHRISTINE HARRIS No. Actually we didn't find an effect of warm up. So if you've just watched a nature film or if you've just watched a comedy it doesn't affect how much you laugh or smile in response to tickling. And vice versa, if you are tickled and then watch a funny film it doesn't increase the amount of laughter.

ALAN ALDA Did it seem similar to you to the laughter you had when you were laughing at the tape?

MARGARET Not at all. No, it didn't seem humorous to me. I mean the squirmy feeling is the reaction, but it wasn't the same sensation evoked by the video.

ALAN ALDA (NARRATION) Which brings us to the biggest little tickle question of all -- just why are we ticklish? Christine Harris thinks it might help develop combat skills.

HARRY I got you. Adam, I got you. You can't get away!

ALAN ALDA (NARRATION) The laughter keeps the tickler tickling even while the tickled is trying to escape.

CHRISTINE HARRIS It looks like you're having the time of your life, you look like you're loving it, you're laughing and smiling, but a lot of people don't actually like to be tickled.

ALAN ALDA Do you?

CHRISTINE HARRIS No, I don't. I don't, no.

ALAN ALDA (Laughs) You don't seem to like to talk about it...

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## LAUGHING MATTERS

ROBERT PROVINE OK, we've got another experiment for you. This has to do with the little boxes on your desk. Ready? OK, push the button.

ALAN ALDA (NARRATION) All that tickling got us thinking about laughing. So we dropped in on Bob Provine's class at the University of Maryland with another of our deceptively simple little questions: just what is laughter?

ROBERT PROVINE OK, well I think it's undeniable that laughter is a really powerful sound. You didn't decide to laugh, you just laughed when you heard the laughter. There's something special about that sound.

ALAN ALDA (NARRATION) Laughing just happens to be one of my favorite activities -- so I'm more than happy to provide a laugh for Bob's computer.

ROBERT PROVINE You notice how much more regular that was than speech. So as I speak in to the computer here, we see that there's a very irregular pattern as opposed to those regular hills and valleys that were separated by regular intervals when we laughed. For example... (laughs).

ALAN ALDA (NARRATION) Bob Provine, as you've probably guessed by now, is a laughter expert.

ALAN ALDA Have you seen anybody about that?

ROBERT PROVINE Ahhh, there's no known treatment for it.

ALAN ALDA (NARRATION) He's listened to laughter from cultures around the world and always finds this characteristic pattern of regular peaks and valleys.

ROBERT PROVINE And in fact it's very difficult to laugh in other than that regular way. For example, could you laugh really fast.

ALAN ALDA Laugh really fast.

ROBERT PROVINE A high speed laugh. (Laugh)

ROBERT PROVINE OK, we still have the peaks and valleys.

ALAN ALDA Yeah.

ROBERT PROVINE But that's not much faster than what we were doing. Try to laugh faster.

ALAN ALDA (Laugh) A little sinister there.

ROBERT PROVINE Try one more.

ALAN ALDA (Laugh)

ROBERT PROVINE I'm not too proud to do this, so you don't be.

ALAN ALDA (NARRATION) Provine argues that not only is human laughter highly stereotyped -- it also sets us apart from all other animals.

ROBERT PROVINE The chimpanzee laughter is like this: aha, aha, aha, aha. And if in fact you were tickling a chimpanzee and rolling around in a little rough and tumble play with a chimpanzee, which is what we've done as part of our research, that chimpanzee will perform what's called a play face and make that sound. And you would be absolutely convinced that that is laughter, even though the sound's a bit different. But the sound is not just different; it's different in a way that makes a huge difference. It's a difference that reveals to us why we can talk and chimpanzees can't. You know, when I laugh, I'm going ha, ha, ha -- I'm chopping an outward breath. Well, chimps don't do that -- can't do that.

ALAN ALDA And why?

ROBERT PROVINE Chimps laugh by going aha, aha, aha. Their laughter is locked in to their cycle of breathing.

ALAN ALDA So it's both in and out.

ROBERT PROVINE Yeah, it's in and out.

ALAN ALDA And they can't chop off an expulsion of air, they can't take an exhalation and chop it into discrete bits.

ROBERT PROVINE Yeah, that's exactly...

ALAN ALDA The way we can. What is there about us that enables us to do that?

ROBERT PROVINE Well. I was puzzling about this for a long time. And our most recent work has indicated that it's being able to stand up and walk on two legs.

ALAN ALDA (NARRATION) When a four-legged animal walks or runs, its breathing is literally locked in step with its stride. Only humans, Provine argues, whose forelimbs no longer support weight, can breathe freely.

ALAN ALDA So the ability to stand up, however that derives, also conferred on us the freedom for our lungs to now be directed, used in other ways. I mean, was that automatic? Do you suppose that people automatically started laughing? Ho, ho, look at this, ho, ho. I mean, how do you get from being able to stand up, do you suppose, to actually producing these staccato sounds?

ROBERT PROVINE Being able to walk upright on two legs is the necessary event but not sufficient. So when you walk upright on two legs this means there can be selection for the fancy sound making we call speech.

ALAN ALDA (NARRATION) So according to Provine, the regular sounds of laughter allowed our ancestors gradually to evolve the irregular patterns of speech. A nice idea. But what's laughter for today?

ROBERT PROVINE Laughter is really not about jokes, it's not really about comedy...

ALAN ALDA Now you tell me!

ROBERT PROVINE It's about relationships between people.

ALAN ALDA (NARRATION) Laughter, he argues, is a sort of social lubricant, occurring thirty times more often when people are in groups than when they're alone...

TWO GIRLS We always laugh together.

ALAN ALDA (NARRATION) ... and often for no obvious reason.

ROBERT PROVINE Laughter is an unconscious response, and we don't have complete control of it. Good actors can simulate a laugh. But like you can't cry on command, most people can't laugh on command and it's very apparent when they do so.

MAN Laugh? (Fake laughter) Oh my god, that was funny!

ROBERT PROVINE In fact, if you ask a person to laugh, their first response will be well. I can't laugh on command, I can't just laugh because you ask me to.

WOMAN Just make yourself laugh, huh?

INTERVIEWER Yeah.

WOMAN I guess I can't do it.

YOUNG MAN Laugh? I've got to think of something funny now.

FIRST CANADIAN Well, you see, we're Canadian...

SECOND CANADIAN Yeah, we're Canadian, we're not able to spontaneously laugh like that. You know, quiet, reserved...

ROBERT PROVINE And of course, after that they may laugh, ha, ha.

ALAN ALDA They're laughing then not because you asked them to, they're laughing because of some social glue they're hoping to exude.

ALAN ALDA (NARRATION) And then there's another kind of laughter -- the nervous giggle that can inflate to the verge of hysteria.

GIRL Someone make a joke or something...

ALAN ALDA I saw somebody laugh for half an hour because we were right next to the cliff. And it was ha ha, ha ha -- what's the matter -- nothing, I'm fine. Or seeing a snake, you know, I see a snake, there's a snake -- are you OK -- no, I'm fine, it's just a snake, I'm OK. Now that sound like it's taking us back a good 200,000 years, or a million years, to somebody who's upright and scared.

ROBERT PROVINE I think we overestimate how reasonable we are, and in laughter we're penetrating beneath that veneer of civility and language and rationality into something that's very primitive, very deep and we share with other animals. So just as we go to the zoo and hear other animals make various calls and cries, when we examine our own laughter it's exactly those kinds of sounds.

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COLD COMFORT

ALAN ALDA The questions pop into our heads every time it happens. Along with the unexpected sneeze or the suddenly scratchy throat, we wonder, how did I catch it this time? How bad is it going to be? Should I take some vitamin C, suck a lozenge, drink some herbal tea? And then there's the big one. If scientists can send a man to the moon or invent the Internet or peer at distant galaxies, why can't they cure the common cold? Well, I've come here to Charleston, South Carolina, to find out. Because Charleston is about to experience a sudden mini-epidemic, an outbreak of runny noses and stuffy heads that could take us one step closer to an answer.

ALAN ALDA (NARRATION) What's unusual about this outbreak of colds is that it didn't just happen.

NURSE Put it in the cup. In the cup. In the cup.

ALDA (NARRATION) These volunteers, whose noses are being rinsed out with a saline solution, are being paid to catch a cold.

ALAN ALDA If you wash his nostrils out he'll have a better chance of catching cold?

BARBARA WRIGHT Mm, mm. 'Cos the nose'll be nice and clean.

ALAN ALDA This is a horrible thing to learn first thing in the morning. OK, go ahead. I mean I would have thought that getting your nose clean -- like, you know, they say, keep your nose clean -- I would think that would help.

ALAN ALDA (NARRATION) The man dispensing the colds is Ronald Turner, an old hand at conducting studies on candidates for cures. What he's carefully placing up the nostrils of his volunteer subjects is a strain of rhinovirus, one of the commonest causes of the common cold.

ALAN ALDA Now you already had one of these?

ANNE SANDERS I had one. I had one already.

ALAN ALDA So how many do you give?

RONALD TURNER Two. We just go around twice.

ALAN ALDA You really want to make sure you make these poor people sick.

RONALD TURNER OK, this is the same as before.

ALAN ALDA (NARRATION) Actually, Ron Turner is hoping some of his volunteers won't get sick...

RONALD TURNER Here we go again.

ALAN ALDA (NARRATION) ...because for the last two weeks some of them have been taking twice-daily doses of one of those herbal extracts that a lot of us believe helps fend off or shorten a cold.

RONALD TURNER Some are getting active medication, some are getting placebo. Everybody gets the virus.

ALAN ALDA Now do you know, are you aware of who's getting the placebo and who's getting the medication?

RONALD TURNER No, we're all blinded.

ALAN ALDA You don't have any idea?

RONALD TURNER No.

STEVE SCIBELLI This is what they look like.

ALAN ALDA The famous ju-ju bead medication. So what do you think is in there?

STEVE SCIBELLI I'm really not sure. Hopefully some medication that will take care of me. But for all I know it could be just sugar pills.

ALAN ALDA (NARRATION) This need to ensure no one knows who's getting what is absolutely critical in a trial like this. It's especially important that the volunteers aren't picking up any clues from how the pills taste or make them feel.

RESEARCHER Do you think you were getting the active medication or the inactive medication?

ANNE SANDERS I think I was getting the inactive.

ROBERT BOZARD I have no idea. I really don't. I had no side effects, no symptoms of any kind either way, so...

RESEARCHER OK, give me a guess.

ROBERT BOZARD Active.

RANDREA MAJORS Inactive.

DAVID MIN I think I was getting inactive.

EDDIE GORDAN Active.

RESEARCHER And why?

EDDIE GORDAN I don't know. It was just that whenever I took it I felt, like, fuller.

MIKE LEWIS I have no idea. I'll have to say the active medication.

RESEARCHER Why would you say that?

MIKE LEWIS It'd kind of depress me if I was having the other medication.

LINDSEY DUGAN I would say the inactive.

RESEARCHER Why would you say that?

LINDSEY DUGAN Just because I didn't feel any difference.

ALAN ALDA Do you think it matters whether or not you believe you're taking the active ingredient?

LINDSEY DUGAN Yes. I think if I thought I was on it, I would definitely experience a placebo effect and feel better than maybe I should. And thinking that I'm not on the medication I might be more inclined to feel the symptoms more severely.

ALAN ALDA (NARRATION) Lindsey's right: if people are able to figure out what they're getting, then it could dramatically influence the results of the trial.

STEVE SCIBELLI I'll go with active.

RESEARCHER Why do you say that?

STEVE SCIBELLI I'm hopeful.

ALAN ALDA (NARRATION) In fact, in Ron Turner's opinion, many of the clinical trials of popular cold remedies are fatally flawed by this very problem. His list includes even that old stand-by vitamin C -- and, distressingly, two of my personal favorites, zinc lozenges and echinacea. He's tested both in carefully controlled trials like his current one, and found they don't work.

ALAN ALDA All right. I've got one left. If you kill this, I'm never going to be able to fight off a cold again. Vitamin E.

RONALD TURNER Well, vitamin E is interesting, and we've looked at vitamin E as well. There's some biologic rationale for vitamin E, and for vitamin C for that matter, in the sense that they are both anti-oxidants, and we do think that oxidative stress in the cell has something to do with production of the symptoms of the cold. And so we did a study of vitamin E, where we gave vitamin E supplements for a couple of weeks to a group of volunteers. We drew blood from 'em, we showed that the vitamin E levels in their blood were substantially higher than in the placebo group, and then we challenged them in our model with our virus and had absolutely no effect.

ALAN ALDA So it was no good as a prophylactic, but...

RONALD TURNER Or as a treatment.

ALAN ALDA Or as a treatment either?

RONALD TURNER Right.

ALAN ALDA I'm dead. That's it. I've got nothing left.

RONALD TURNER Well the good news is that you'll get over your cold anyway.

CAROLINE SWAIN Definitely have the cold. The cold, I have it.

MIKE LEWIS I don't feel ill at all. If I'm supposed to be ill right now, I'm not ill.

UNKNOWN I have the cold.

ALAN ALDA (NARRATION) Three days have passed since our volunteers were infected with the cold virus. They've been reporting in every morning since.

RESEARCHER It's been about 72 hours since the inoculation. Do you think you received a cold?

STEVE SCIBELLI Yeah, I do. I definitely had it yesterday.

RESEARCHER OK, I want you to rate your symptoms this morning, based on the severity since your last visit. Any symptoms of sneezing?

STEVE SCIBELLI I'd say about a two.

RESEARCHER OK. Runny nose?

STEVE SCIBELLI One.

RESEARCHER Nasal stuffiness or obstruction?

STEVE SCIBELLI Two.

ALAN ALDA (NARRATION) There are a dozen symptoms on the list -- enough to get a pretty objective measure of the severity of the cold.

RESEARCHER Definitely getting a little bit worse, huh?

STEVE SCIBELLI Yeah.

RESEARCHER OK, you can go on back and get your nasal wash.

ALAN ALDA (NARRATION) The nasal wash will reveal how strongly the virus took hold. Meanwhile we wondered how our volunteers feel now about whether they are on the test medication or the placebo.

ANNE SANDERS I think I'm receiving just a placebo. (P)

DAVID MIN I think it kind of got better because I was taking... I'm not sure whether I had that medication or not, but I think I did. (P)

EMILY WORREL I believe I had the inactive medication. Because otherwise I think I wouldn't have got the cold or it wouldn't have been as severe. (P)

KATHERINE HOEFT Based on how mild my symptoms are, I think maybe I did get the active. (A)

RANDREA MAJORS Oh, yeah, I'm really glad I got it. Otherwise I'd be walking around with tissues hanging out of every pocket, and just not a pretty sight. (P)

LINDA MIELCAREK I think I got the inactive medication because I've been getting worse as the days go on. (A)

LINDSEY DUGAN I guess I got the active medication, 'cos all I've had is a runny nose and that's it. (A)

ALAN ALDA (NARRATION) Perhaps not surprisingly, most of those with the worst colds thought they were on the placebo, while most subjects with mild

colds guessed they had the medication. But in fact it was all in their heads. Later, when who got what was matched up with the severity of their infections, there was no difference between those who got the test substance and those who didn't. That's right, the mystery herbal ingredient in those big brown pills did nothing in Ron Turner's study -- joining on his hit list echinacea, zinc lozenges and vitamin E.

ALAN ALDA You know what's funny about this? And this is just totally personal. I'm going to keep taking this stuff, because I haven't got any other feeling of control over the cold. And for me getting a cold, because I have to use my voice in my work, is something that... I'll clutch at straws. How does that strike you as a scientist?

RONALD TURNER Well, I guess I don't have any problem with that. As I said, my job here is to try to figure out whether there is a biologic effect. Whether people choose to use that information or whether they get some benefit -- whether it's psychological or mental -- that's fine. You know, the saying is of course that if you take this medication you'll get over your cold in 7 days and if you don't it will take a week. So...

ALAN ALDA That's the best you can come up with? After all these years?

RONALD TURNER Well, I think we're doing better than that. I think we're doing better than that.

ALAN ALDA (NARRATION) One way in which science may at last be doing better is in attacking cold viruses themselves. A big reason the common cold hasn't been cured in the past is that so many different viruses can cause it.

STEVE WORLAND And for many, many years, people thought that was going to make it impossible to develop therapy for the common cold.

ALAN ALDA Yeah, that's what I've read, constantly, that there's too many colds, too many viruses, to be able to find something common in all of them.

STEVE WORLAND Right. And I remember when I first started on this project, somebody who I was good friends with in college who -- we diverged slightly, he went into medicine and I went into basic biochemistry -- I told him I was working on this and he laughed his head off. He said, there are over a hundred serotypes, no one will ever do that.

ALAN ALDA Now your friend is giving out anti-histamines and you're solving the common cold!

ALAN ALDA (NARRATION) Steve Worland's company, Agouron, is trying to attack the commonest group of cold viruses, the rhinoviruses. Their target is actually a protein called protease, that all rhinoviruses use to make copies of themselves. The company started by making tiny crystals of this crucial protease, then used an X-ray crystallography machine to get a precise three-dimensional picture of it.

SCIENTIST The X-rays are generated right here, and if you stand up you can see the tip of the loop, the crystal is very small, only a couple of tenths of a millimeter. What we're seeing here is an electronic image...

ALAN ALDA (NARRATION) Now, there are moments, when we're making Frontiers, when we get just a little out of our depth.

ALAN ALDA What do you do, roughly, to get a three-dimensional picture from these dots?

SCIENTIST Well, basically what we do, we use computers to carry out a three-dimensional Fourier summation, and the individual coefficients in that Fourier series are related to the intensities we're measuring here.

ALAN ALDA And that's the rough version.

ALAN ALDA (NARRATION) OK, well once they did that, this was the result, a 3-D image of the protease the virus needs in order to replicate itself in our nose cells.

STEVE WORLAND That was enough to say that there are regions where the protein goes in rather than comes out where we can plug in, if you will, our drug molecule.

ALAN ALDA The reason you want to plug your drug molecule in is that if you don't do that, this is going to be a place where the protease is going to hook up with what it needs to hook up with to do its work and help the virus to replicate.

STEVE WORLAND That's precisely right.

ALAN ALDA (NARRATION) The drug molecule Agouron designed, which nestles neatly into the critical protein, successfully stopped the virus from replicating in a test tube. The next step was to try it in noses.

NURSE Good morning everybody.

ALAN ALDA (NARRATION) In a clinical trial very similar to the one Ron Turner ran, the anti-viral drug was tested on college students at the University of Virginia -- except that here the subjects got to stay in a hotel. Twenty-four hours after getting infected, they received several daily doses of the experimental drug in a nasal spray. Here too, some of the subjects got a placebo spray instead of the real thing.

NURSE Do you feel generally bad?

SUBJECT I feel like I've got a cold.

NURSE OK. That's what I need to know.

ALAN ALDA (NARRATION) The severity of their colds was judged by questionnaire, by measuring the virus directly, and by weighing the tissues they used. And the results were promising -- a significant reduction in cold symptoms among those on the drug.

NURSE How you feeling this morning?

SUBJECT I'm doing fine.

NURSE No cough, no sore throat, no nothing?

SUBJECT No.

NURSE All right. That sounds good.

ALAN ALDA (NARRATION) Even though the drug seems to work, getting it to market will be far from easy. It will have to be cheap; it will have to work fast; and, as Steve Worland knows only too well, it will have to be completely safe.

STEVE WORLAND It's a real drag to have a cold, but it's not life threatening. And so in that case we're even more concerned about a safety burden because we're not treating something like cancer or HIV where a certain degree of side effects traded for saving somebody's life, that person would almost always say, I'll take it.

ALAN ALDA It's not worth trading a serious side effect to get rid of a cold.

STEVE WORLAND Exactly. So this really has to be a compound with virtually no side effects or people are just going to elect not to take it. If you tell people, well, you know, you're going to feel numbness in your hands, just as a hypothetical example, but your cold will go away, most people will say, I'll take the cold.

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## WHY ARE PEPPERS HOT?

ALAN ALDA (NARRATION) Our next little question brings us to Santa Fe, New Mexico, and a food festival celebrating what's practically the state food - the chile pepper. The question is of great personal interest to me. But it isn't one you'd imagine leading to a medical breakthrough.

ALAN ALDA So here's the question: Why are peppers hot? Well, why are they hot?

PAUL BOSLAND Chiles are hot because they have a compound, or a set of compounds, called capsaicinoids that's found inside the fruit, along the placenta. And contrary to a lot of beliefs, the walls have no heat, the seeds don't have any heat, they're only in this one little area here - where this orange coloring is? - that is the capsaicinoids. So the more orange, the hotter the chile.

ALAN ALDA (NARRATION) My hosts' plan is for me to sample some of the different peppers here so that I can appreciate their subtleties. But for me subtlety and peppers don't mix. So offered a choice of mild, medium or hot...

ALAN ALDA Let's get hot right away.

DAVE DEWITT OK, this is the *Capsicum picatum*, I'll let you try this. Also known as aji in South America.

ALAN ALDA It's good.

DAVE DEWITT Now you said you liked hot peppers.

ALAN ALDA Yes I do.

ALAN ALDA (NARRATION) I'm not the only one here playing with fire. Paul and Dave are still determined to teach me the fine art of pepper tasting. But I get the horrible feeling it's already too late.

PAUL BOSLAND The three areas to look for is the front of the mouth, mid mouth and the back of the throat, the throat area.

ALAN ALDA Tastes like oatmeal. I don't taste anything.

DAVE DEWITT Oh, we burned your taste buds with the hot one...

PAUL BOSLAND Well let's try this one. We'll see what happens here. It's a little hotter now.

ALAN ALDA OK...Tomato sauce.

PAUL BOSLAND Aargh!

DAVE DEWITT We burned you out, that's what the problem is. It may be several hours before your palate gets back to normal.

ALAN ALDA Why are we in red light like this?

ALAN ALDA (NARRATION) Burned out my palate? This sounds serious -- which is why I find myself sitting in a very strange room in Baltimore.

ALAN ALDA This is very futuristic.

SYLVIA KING Yes it is.

ALAN ALDA Oh look, there are little screens down there.

ALAN ALDA (NARRATION) I've come here to check my heat-sensing abilities against some of the best-trained tongues in the world, belonging to the members of the pepper-tasting panel at one of the nation's largest spice companies, McCormicks. Sylvia King is in charge.

SYLVIA KING Everybody get set, and go.

ALAN ALDA (NARRATION) We start with what's reckoned to be a mild solution of the hot pepper chemical capsaicin.

SYLVIA KING Swallow.

ALAN ALDA (NARRATION) We're instructed to assign it a five on a heat scale of zero to fifteen.

SYLVIA KING So is everybody ready? Rinse with water and rinse with a cracker.

ALAN ALDA (NARRATION) A cracker, hmm? What happened to the sour cream?

ALAN ALDA Does the cracker really clear out the sensation of heat?

SYLVIA KING It will help. Get ready for your strong reference.

ALAN ALDA (NARRATION) The idea here is to tune our tongues to a standard set of heats -- concluding with a dose of capsaicin scoring a respectable 13 on the heat scale.

ALAN ALDA Smooth!

ALAN ALDA (NARRATION) OK, with our tongues now calibrated, it's time to see how we all rate a sample from a real hot pepper -- which is why, by the way, the light's red -- to disguise the sample's color, so it won't influence our score.

SYLVIA KING Set and go.

ALAN ALDA (NARRATION) I'll give it an 8. And my fellow tongues?

MARIANNE GILLETTE I would give it about a 7.9

OTHER TASTERS 7.5...about a 7...7.2...about a 7.6...

ALAN ALDA (NARRATION) Well that's a relief. My tongue seems right in line with the experts'.

OTHER TASTERS 7.5...7.8...7...about an 8.2.

ALAN ALDA I'm sort of amazed that I even could taste anything in the mild one, you know. I was really afraid when I came in here you'd say this is the mild one and I'd say, no that's water!

ALAN ALDA (NARRATION) Of course, the spice company didn't set up the heat-sensing panel just for my peace of mind. It's one of several ways they check the heat of all the peppers they buy, so that their customers don't get a nasty surprise once the pepper's ground into powder or flakes. Still, heartened that my tongue has survived years of hot pepper pummeling, I took it to a specialist.

ALAN ALDA So if I can taste this as extremely bitter I'm a...

LINDA BARTOSHUK A supertaster.

ALAN ALDA I'm a supertaster. If I can't taste anything...if it tastes like a piece of paper...

LINDA BARTOSHUK You're a non-taster.

ALAN ALDA Oh boy.

LINDA BARTOSHUK And if it's something in the middle, you're a medium taster. Be sure the paper gets really moistened with your saliva and moves all around so it covers your whole tongue. Are you tasting anything?

ALAN ALDA It's bitter.

LINDA BARTOSHUK Ah yes, yes. Authentic supertaster.

ALAN ALDA It's really bitter.

LINDA BARTOSHUK Oh oh, alright, I think now's the time to take it out.

ALAN ALDA If I'm not a supertaster, I don't want to know. This is close enough.

ALAN ALDA (NARRATION) Only one person in four is a supertaster...

ALAN ALDA Blech!

LINDA BARTOSHUK I can't share that experience with you because I'm a non-taster.

ALAN ALDA (NARRATION) While another one in four, like Linda, doesn't taste the paper at all. The paper was only the beginning of my tongue check-up - next came blue food coloring.

LINDA BARTOSHUK OK, swallow. Move your tongue in your mouth a couple of times and swallow a couple times, and that will distribute the dye. And then we'll have a look. Stick your tongue out. Oh, magnificent, the staining is absolutely perfect, I can see the pink fungiform papillae. Your tongue looks like it's tiled in fungiform papillae. You definitely look like a supertaster.

ALAN ALDA I'm a supertaster.

ALAN ALDA (NARRATION) The fungiform papillae are little sprouts on my tongue. Each one harbors a half-dozen or so taste buds, with nerve fibers connecting them to my brain. While some of these fibers convey the sense of taste, most of them don't sense taste at all, but pain. Which brings us back to hot peppers.

LINDA BARTOSHUK You are feeling way more pain from eating a red pepper than I would, for example.

ALAN ALDA Because I have more of these structures.

LINDA BARTOSHUK That's right. You have way more pain fibers so you perceive way more pain.

ALAN ALDA This is really weird because I eat far more red pepper on my food than anybody I know.

ALAN ALDA (NARRATION) Now of course it may be that I just like pain more than most people. But there's another explanation, which goes back to that hot pepper I ate in Santa Fe. Because it not only knocked out my sense of taste. After the initial burn, it actually numbed the pain fibers that nestle around my taste buds.

ALAN ALDA Now that this is cooled a little I put the pepper in?

ALAN ALDA (NARRATION) Which is why I'm helping make hot pepper candy. A dash of cayenne pepper before the traditional taffy pull...

ALAN ALDA Both thumbs, I have both thumbs in the taffy. I can't get my thumbs out of the taffy.

ALAN ALDA (NARRATION) And the result is a candy that Linda Bartoshuk uses to treat patients with painful mouth sores. The candy was the idea of a student of hers, but others had thought of it before.

LINDA BARTOSHUK If you go back and read accounts of Aztec medicine, you'll find out that the Aztecs were using chile peppers mixed with honey to treat sores in the mouth. My guess is that every culture that has ever consumed these chile peppers has figured out that they are really good analgesics. We're just the last in a long line of people who've looked at that.

ALAN ALDA (NARRATION) One man who's that happy researchers are again exploring the pain-killing properties of peppers is a long-term survivor of AIDS, living in San Francisco. A few years ago, he began suffering agonizing pain in his feet due to a condition known as neuropathy.

GEPPETTO The pain was very, very deep inside my feet, just underneath the toes. The best way I can describe it was that there was broken glass in there, on the nerves, to the point my life was just becoming very sedentary.

ALAN ALDA (NARRATION) An active runner and volunteer with the AIDS quilt project, Geppetto Apodaca became housebound, his pain controllable only with powerful drugs.

GEPPETTO I thought that if this pain continues, and if all they can do for me is tranquilizers, then I just didn't want to go on any further. And that's pretty much where I was until I met the pain management crew and Wendye Robbins.

WENDYE ROBBINS An interesting day to be doing this from a symbolic perspective. This is the start of the Jewish calendar.

ALAN ALDA (NARRATION) Wendye Robbins, an anesthesiologist, figured if hot peppers numb pain in the mouth, why not elsewhere?

WENDYE ROBBINS That was part of the originality of the invention, was realizing that the same nerve fibers that are present in the mouth and signal hot or spice when we eat them are also present on the foot and therefore can probably be interacted with in the same way.

ALAN ALDA (NARRATION) Geppetto's treatment begins with a powerful local anesthetic smeared on his feet.

WENDYE ROBBINS Before we put capsaicin on him we have to make sure he's pretty numb. Otherwise the capsaicin itself would be exquisitely painful.

ALAN ALDA (NARRATION) The mask protects against the fumes from the capsaicin cream.

WENDYE ROBBINS This is a hundred fold more potent than the stuff that's available commercially. This is 7.5% by weight. If I was to touch this to your foot, or to the foot of anyone else who wasn't anesthetized, it would be excruciatingly painful.

ALAN ALDA (NARRATION) While we wait for Geppetto's feet to bake, we've time for a quick visit with another team of San Francisco scientists. With research materials bought from local supermarkets, their goal was to find the molecule in our bodies that responds to peppers' heat. Among the peppers David Julius and Michael Caterina tested was the habanero, the hottest of all.

DAVID JULIUS Very pungent. Tearing my eyes. Making it a little hard to breathe. All for science, you know.

ALAN ALDA (NARRATION) What the researchers have found is the molecule in our nerves that hot peppers activate when they cause their painful burn. The molecule sits like a trapdoor on the surface of the pain fiber. Capsaicin unlatches the door, allowing calcium ions to rush in -- and so firing off the pain message to

the brain. Here's what happens when capsaicin is added to living cells that are cued to light up when the trapdoor opens.

MICHAEL CATERINA If you were to take the neurons that normally respond to pain in our bodies and subject them to this same sort of assay, this is exactly what they would look like. They would start off purple and then when you added capsaicin to them, they would all light up. A silent scream.

ALAN ALDA (NARRATION) The researchers discovered that very hot water also makes cells give this same response. In fact, the original job of the trapdoor molecule in our bodies may have been to detect and warn of dangerous heat. So here's the ultimate reason peppers are hot - capsaicin fools our cells into thinking they're on fire! Right now Geppetto's feet know the feeling only too well.

GEPPETTO I'm beginning to feel a very, very, very hot sensation on my feet right now.

ALAN ALDA (NARRATION) But just as the hot pepper candy relieves mouth sores, so Geppetto's much more dramatic treatment should relieve his much more devastating pain - once the burn wears off.

GEPPETTO The first time we did it, my initial feeling when I got home was that the pain was so bad from the capsaicin that I couldn't realize that it was going to get any better. And as the third day came around and I was able to put on shoes comfortably for the first time, it was like being born again.

ALAN ALDA (NARRATION) This time Geppetto was running again within the week - and if his previous treatments are a guide, he'll remain virtually pain-free for months. Meanwhile, Wendye Robbins hopes that many other patients with debilitating pain can also be treated with pepper's chemical heat.

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## GRAINS OF INSPIRATION

ALAN ALDA The beach is a great place for thinking up trivial questions. For instance, have you ever noticed that when you walk in wet sand, the color of the sand seems to change in a sort of halo around each footprint? Why is that? It's no coincidence that this particular little question popped up here, on the shore of Lake Michigan in Chicago, because at the University of Chicago are a couple of scientists who just love asking trivial questions about stuff like... well, stuff like sand. You really do love sand, eh?

SIDNEY NAGEL Of course, it's one of the best substances there is.

ALAN ALDA What about my question. Why do we get this sort of halo around our footsteps when you walk on wet sand?

SIDNEY NAGEL What we've got here is sand in this squeeze bottle. And we've filled it with water to a little bit higher than the level of sand. And so, as I squeeze this, what's going to happen? Normally you would think that everything is just going to rise. But as you saw with the sand near the lake, you squeeze it and the water drops below the level of the sand.

ALAN ALDA That's great. You let go of it and the sand goes down and you have a layer of water on top. You squeeze it - look at that water, it seems to go all the way down there and the sand goes right up

ALAN ALDA (Narration) The explanation's actually simple. Squeezing the bottle makes the sand grains move past each other -- and to do that, they must first move slightly apart. The water then runs down into the bigger spaces between them. On the beach, my weight pushed the sand grains apart, and the water draining away created the haloes. In fact, whenever grains move, they must first move away from each other. For instance, only the seeds on the surface of this avalanche have the room to expand and so to flow. And it's when sand flows that it really gets interesting.

ALAN ALDA What is this orange thing?

SIDNEY NAGEL This is a puzzle, which has orange sand in this plastic tube, and in the middle of the sand we have this big steel ball. And the question I have for you is, the ball is on one side and I want you to get the ball over to the other side of the container.

ALAN ALDA OK, so the ball is on this side, I have to get the ball to this side of the sand, eh?

SIDNEY NAGEL That's the idea.

ALAN ALDA OK, so the first thing obviously is to try to shake it.

ALAN ALDA (Narration) Obvious perhaps -- but equally obviously, not effective. Stubbornly, the ball refuses to sink.

SIDNEY NAGEL Suppose you try it upside down?

ALAN ALDA It's climbing right up! There it is, there it is, it's right at the top. OK, what makes it climb up through the and like that?

HEINRICH JAEGER Great question. And to answer that, we're going to the lab.

ALAN ALDA (Narration) The lab we're heading for is the University of Chicago's Materials Center.

SIDNEY NAGEL So this is the two dimensional version in a real laboratory situation of what you saw here.

HEINRICH JAEGER Let's just turn this thing on.

ALAN ALDA Look at that, wow! And there it goes, down the side. I was just going to say, I can see poppy seeds moving down here.

SIDNEY NAGEL But this big one can't make it, can it?

ALAN ALDA No.

ALAN ALDA (Narration) The only thing going on here is that the container is being briskly shaken up and down. It's a fancy version of what can sometimes happen if you shake a can of mixed nuts. The shaking un-mixes them, causing the large nuts to rise to the top. Remarkably, there's never been a good explanation for this phenomenon. But a clue came from that thin downward stream of grains I'd noticed along the wall. Here's what Sid and Heinrich think is happening. As the grains are thrown upward, those nearest the wall are dragged against it, slowing them down. When the grains fall, they're less densely packed, so there is less drag against the walls. The result: the grains next to the wall slowly move downward, setting up a sort of convection current. The current rises in the center, carrying everything with it. But at the walls the current is too narrow to take large objects down again, so they are left stranded at the top. In a shaken can of mixed nuts, the Brazil nuts present themselves ready for eating. All very interesting, but...

ALAN ALDA Suppose mixed nuts is not the most important thing in your life. What else does this apply to, anything? Or is it great that we have this understanding of how particles move?

SIDNEY NAGEL Mixing is a terribly important thing in the pharmaceutical industry. That is, if you are making pills out of various powders, you want to mix them. And if you don't mix them properly, then you'll have some pills that have all the binder and other pills that have all the good stuff, but having all the good stuff in one pill is very, very bad.

ALAN ALDA You could kill somebody.

SIDNEY NAGEL You could kill somebody with that.

ALAN ALDA (Narration) A great example of how an apparently trivial question can lead to a very non-trivial answer. One of Sid Nagel's favorite little questions confronted him one day from his kitchen counter.

ALAN ALDA Are these historic coffee stains here? Are these the ones that gave you your inspiration?

SIDNEY NAGEL Oh, they're a day old or so. But when they're as lovely as this, wouldn't you have trouble wiping them up?

ALAN ALDA (Narration) Yes, it's true, Sid really does find coffee stains beautiful - because they made him wonder why, when a coffee spill dries, it always leaves a ring. Enough of Sid's colleagues took the question seriously that experiments began to watch what happens as a coffee spill dries.

SIDNEY NAGEL So Rob here has been looking under a microscope at some of the drops that instead of using coffee we've used particles that you can visualize under microscopes.

ALAN ALDA I'm seeing a lot of particles moving from over here to the edge.

ALAN ALDA (Narration) The question was, what's causing this flow? The answer hinged on the fact that the edge of a spill becomes pinned in place by tiny rough spots on the surface, so the edge can't pull back as the liquid evaporates. As the edge loses liquid to the air, it has to be replenished by liquid from within the drop - and the flow that results carries with it the tiny suspended particles.

ALAN ALDA Is this white band particles that have built up on the edge already?

SIDNEY NAGEL That's right. And so you see how slowly and carefully they come in there and they pack very nicely into a very well packed, almost crystalline ring.

ALAN ALDA (Narration) The careful packing means that even this humble discovery could have unexpectedly useful consequences - for instance in manufacturing ultra-fine wires in electronic circuits. So even in coffee stains, there can be inspiration.

ALAN ALDA It's really interesting to me that this kind of stain from a few drops of coffee has probably shown up on countless millions, thousands of millions, of counter tops...

SIDNEY NAGEL On my counter top alone it's shown up that many times!

ALAN ALDA And many of these counter tops were the counter tops of serious, curious scientists. And yet you and the people you work with took these stains seriously and you thought that something can be learned from that that will lead us to a deeper understanding of things other than coffee stains

SIDNEY NAGEL I have this kind of broad view of what physics should be. And it's not just building the big new superconducting supercollider or a new Big Bang theory of the universe. It's also trying to understand phenomena such as this that gives us the feel and texture of our daily lives, and it's just important to understand.

ALAN ALDA It's possible then that by studying things like coffee stains on the counter top and sand in an hourglass or nuts in a container of mixed nuts really can give you some insight into how the whole universe is formed.

ALAN ALDA (Narration) See where wondering even about the little things can take you...?

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