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Challenging Common Knowledge
Inside the mind of physician-economist Bapu Jena

Guest: Bapu Jena
Interviewers: Stephanie Dutchen, Rick Groleau

STEPHANIE DUTCHEN: Hello and welcome to the August 2016 Harvard Medical Labcast. This podcast is brought to you by Harvard Medical School's Office of Communications in Boston. I'm Stephanie Dutchen.

RICK GROLEAU: And I'm Rick Groleau.

DUTCHEN: So Rick, tell us what today's abstract is about.

GROLEAU: Well, it's about research being done on oocytes, which are immature egg cells. And the topic inspired me to write a couplet. Would you like to hear it?

DUTCHEN: Uh-oh.

GROLEAU: I'll take that as a yes. Here goes:

The term amyloid is a source of unease,
'Cause it's often connected to some brain disease.
But within the germ egg cell called oocyte,
It's needed to keep organelles packaged tight.

DUTCHEN: [LAUGHTER] Very nice, Dr. Seuss.

GROLEAU: Well, thank you very much. Okay, and then in today's conversation, you'll be taking us inside the mind of Bapu Jena. Tell us more.

DUTCHEN: Yes, so his name is Anupam Jena, but he goes by Bapu. And he is -- now I wrote this down so I would get it right -- the Ruth L. Newhouse Associate Professor of Health Care Policy here at HMS. Which basically means he's an economist, and a physician, and he asks very interesting questions.

So we asked him about how he comes up with those questions that tend to investigate what people think of as common knowledge.

GROLEAU: You mean things that challenge common knowledge?

DUTCHEN: Well, sometimes what he finds agrees with what people think and sometimes it doesn't. And he told us things like what was the weirdest place that he's ever come up with an idea, and how to shift your mindset from solving a problem that's given to you, to finding a problem to solve.

GROLEAU: Sounds great. Let's take a listen.

[MUSIC PLAYING]

DUTCHEN: So Bapu, thank you so much for joining us today.

ANUPAM JENA: Thank you for having me.

DUTCHEN: Now, you have quite a collection of studies to your name, and the theme that seems to tie them all together is that you are examining what seems to be common knowledge. People assume that, for example, doctors are more likely to be divorced than people in other professions, or, well, of course when medical students head into the clinic for the first time as interns there's a so-called July effect where patients do worse. And you actually look at whether these things are true. Is that how you think about the kind of work that you do?

JENA: Yeah, I think so. The general rule of thumb that I have for question is not actually whether or not a physician or health policy researcher would be interested in knowing the answer, I want to answer questions that everybody would be interested in knowing the answer. And that they understand why it is that I'm looking into that question.

DUTCHEN: So how do you choose a specific question to look at, then?

JENA: Well, I have a dartboard and I throw darts and I see what sticks.

[LAUGHTER]

JENA: No, I think there's a few criteria. So the first is it has to meet the general interest criteria. Two is that there has to be detailed enough data that allows you to answer the question in a rigorous way. And the third is actually sometimes the most challenging, is that there has to be a credible way of trying to answer the question.

And what I prefer to do -- is what many economists try to do -- is find some source of natural randomization or natural variation that occurs in the real world -- the term that we sometimes use is "natural experiment" -- to try to uncover some of these relationships that might be otherwise difficult to analyze.

DUTCHEN: So in order to find out whether something is true or not, right, you need to have evidence to look at.

JENA: Correct, yeah.

DUTCHEN: And then what do you do once you've identified a question and you found a good source to study?

JENA: Well, first we're thankful, because I'll tell you that out of every study that you hear about or that we publish, there's probably six or seven that we were far more interested in, that we thought were much more promising, that don't actually pan out. And so we're always grateful when we're able to find something that makes sense, for which the evidence is solid enough to make some conclusions, and again which interests people at large.

DUTCHEN: And what are some of the things that you've looked at lately?

JENA: So lately we've looked at -- I'll tell you some things that we have updated since the last work we published about a year ago as well as some things that we're working on right now that have not been published.

About a year and a half ago we did a study which looked at what happened to patients who were hospitalized during dates of major national cardiology conferences. And the idea there was that this is a point in the year when the patient has a heart attack, or cardiac arrest, or something severe from a cardiac perspective, and when they're hospitalized they may get exposed to a different set of doctors than they would otherwise see, because the doctors are away at conferences.

And what we wanted to understand is, well, what impact does that change in the composition of doctors have on patient outcomes? And what we found was that patients actually did substantially better during the dates of those meetings.

DUTCHEN: Patients did better when the highly skilled cardiologists were all at society meetings.

JENA: Exactly, yeah. And which was a very paradoxical finding for us. And the other fact that we found was that rates of a particular procedure, called PCI -- which is percutaneous coronary intervention, it means stenting of the blood vessels that supply the heart -- we found that rates of that procedure fell by about a third.

And we interpret that to mean that, in that setting, that we might be doing too much of these procedures otherwise. That is to say on non-meeting days. And we thought that that was a proxy for the overall intensity of care that was being provided outside of these meeting dates, and that could maybe be the mechanism.

So that was an old paper, an old finding, and we've just kind of reinvestigated that issue and are trying to understand a little bit more about who are those doctors that attend these meetings. And we've tried to do so in a way that I think is innovative;

and that is by looking at whether or not a cardiologist is billing Medicare during those dates.

So it's difficult to get attendee rolls at the meeting -- so otherwise we could get the American Heart Association and the American College of Cardiology to give us a list of attendees, and then we could look in the Medicare data and see whether or not those cardiologists' practice patterns are different -- the ones who attend meetings and the ones who don't.

Well, without that data, how do you look at this? Well, what we've tried to do is basically look into the claims data and see whether a cardiologist bills Medicare on those particular dates of the meetings versus not, and then look at the characteristics of those doctors. And what we find is that the doctors are about the same age, the meeting doctors and the non-meeting doctors: about 50 years old. About the same proportion are men, it's about 95% are men.

But what is different is that the doctors who do not bill during the meeting dates -- meaning the doctors who are likely to be attending these meetings -- they have three times as many publications, twice as many grants in clinical trials. But the clincher is that they also do a lot more stenting across the course of the year, so these are not just doctors who are doing all research and no clinical work, they're doing a lot of both.

And the way we interpret those findings is that it could be that these are doctors who are very procedurally focused, and very talented, and when they see patients they may be more inclined to use those procedures. And it may happen in a place where the benefits no longer outweigh the risks of the procedure. So that's our current thinking on that issue, which is kind of a reinvestigation of study that we did a while ago, but linking it to new data.

DUTCHEN: Are these the sorts of things that it wouldn't be possible or ethical to structure as, like, a randomized clinical trial?

JENA: Yeah, not only would it be unethical to do it, it would be very costly, very time consuming. And that's exactly why I try to look for natural experiments, to try to uncover some of these relationships that are happening in the real world, because of just random, exogenous things that take place, that we otherwise wouldn't think about.

DUTCHEN: It must be tricky then to figure out what is going on, without being able to control all the variables, right? You're making deductions and assumptions, but how do you then check whether those are correct?

JENA: Yeah, that's tough. So I'll give an example of another paper that we're working on now. My wife ran a five-mile race about a month ago, started at the Seaport -- World Trade Center -- and the route passed through Mass[achusetts] General

Hospital. And my daughter and I -- who's 19 months old -- we tried to go watch the race near Mass General, and we couldn't get there because the route was blocked off. Several hours later when I told that to my wife, she said, "Wow, I wonder what happens when patients need to get to the hospital, these routes were all closed, how do ambulances get there?"

And that I thought was a really interesting question, and a question that we can look at, in the same kind of data. And what we've done is we've looked at rates of mortality for patients who were hospitalized on the days of marathons -- looked at about 10 marathons over 10 years, so these are 10 cities -- and then we compare the mortality on those dates to the surrounding identical dates. So if the Marathon was on a Monday in Boston, we compare it to the identical five Mondays before and the five Mondays after.

DUTCHEN: I assume excluding the infamous Boston Marathon a couple years ago.

JENA: Exactly, excluding that, and also you'd want to worry about whether or not you're picking up mortality from people who are running marathons, that that turns out to be a really, really, really rare event. But we focus on Medicare, and we focus on people in Medicare who are generally sick, and so they're not running marathons.

And what we find is that mortality on the marathon dates is about 10 percent to 15 percent higher than on the surrounding dates. And you ask, well, how do you take that and establish some sort of cause and effect relationship there, because you need to know that those patients are similar. Because it could be that the patients who are hospitalized during the marathon days are just different, they're at higher risk of mortality.

And the way you do that is you just show on a series of characteristics of these patients -- their age, their sex, their race, what chronic conditions do they have, why were they hospitalized, what medications did they take if you have that kind of data -- and show that the characteristics of these patients are essentially identical, between the marathon and the non-marathon days.

And that's the type of evidence that we try to bring to our research, because in many observational studies one looks at the treatment and control groups in the study and they look clearly different. And through various types of analyzes those differences are accounted for, but I would argue that they are rarely fully accounted for, and what really should be the gold standard in this type of research is what is the gold standard in randomized control trials -- you have to show that there is evidence of randomization, if you want to try to uncover real relationships in the data as opposed to just associations.

And to answer that question, we see that these patients are identical.

DUTCHEN: Now, when you come up with an answer after doing one of these studies that seems to run against what people think is true, how do you then deal with the fallout?

JENA: The fallout meaning--

DUTCHEN: I don't know, do people push back? Do people--

JENA: Oh, people always push back.

[LAUGHTER]

JENA: Yeah, people push back, and I think that the people who push back sometimes don't fully understand the mechanisms that we've tried to use -- to kick the tires, if you will -- or we haven't done a good job explaining it, one or the other.

But in each one of these studies, when you have this counterintuitive finding, and you're making rather bold statements about something causing something else, you really have to be thorough about the types of analyses that you do, to make sure that what you're finding is not just some spurious association.

So in the cardiology example case, what we showed was that mortality for non-cardiac conditions did not change. So if you think that there's something different about the hospitals during these cardiology meeting dates, and it influences mortality overall, then you would expect to see that mortality for gastrointestinal hemorrhage or for hip fracture would also go down, and we don't find any evidence of that.

So there's different tools like that you can use as an economist to really try and say, "We don't just this think this is an association that we're observing here, we think that this is a cause and effect relationship."

DUTCHEN: How did you come to develop all of the skills and thought processes to come up with question development and ways to analyze this kind of information?

JENA: I think a lot of it's luck. I mean, I'll say I'm really lucky. And two is that my background and my ongoing experiences help a lot. So I have a PhD in economics, which is extraordinary helpful for thinking about these sorts of questions, because economics, among many other things, really prides itself on being able to take study design very rigorously, and try to understand what causes what, as opposed to saying what is associated with something else. And so that background really helps a lot.

And as important as that is, the fact that I'm able to work clinically helps a lot because it helps me come up with questions; it helps me understand what are the

types of outcomes that we should be looking at. What are the ways in which the study designs could be improved, just based on what you see clinically?

So those things help a lot, and then the third thing, which I think is really something that I've learned over the last couple years -- which I never really fully appreciated -- is that the process by which one comes up with ideas can be an active process.

DUTCHEN: How do you mean?

JENA: What I mean by that is the following example: When you take a class in college -- let's say it's a math class or a physics class -- your assignment may be what's called a problem set; it's a set of problems that you have to turn in at the end of the week. And you can get very good at learning how to solve problems. That's a different set of skills than learning how to come up with problems.

DUTCHEN: Ah.

JENA: And the same kind of systematic approach that one would use to learn material and to answer questions, it seems to me that same type of approach could be used to come up with questions. So one thing that I try to do with my graduate students and students -- it's sometimes limited by time but we try nonetheless -- is say, "Okay, let's come up with five ideas every three or four days," and then among those that seem even remotely interesting, talking through how you'd actually carry out that project. And, you know, I think that that's extraordinarily useful, because it forces you to learn how to think creatively.

DUTCHEN: So what is fun for you about doing this kind of work?

JENA: I think the most fun aspects of the work are the thrill that you get when you come up with a question and you start to analyze it and pieces of the puzzle start aligning with what you thought or hoped they would show.

DUTCHEN: How often does that happen?

JENA: That happens probably maybe one out of five times.

DUTCHEN: So actually maybe that's not that bad.

JENA: It's not that bad, yeah. If you're picking good questions it's great, because at the end of the day all that matters is what your successes are, not your failures. But I mean, it's an exhilarating feeling to have a great idea, or to listen to someone else have a great idea -- to be in a seminar or a meeting and to hear someone go up there and say something where you think to yourself, "Wow, I wish I had that idea" -- it feels good. And then to see how they think through the problem, it's really a rewarding feeling.

And the other part of it is that I'm very fortunate that I have a chance to work with a lot of different people with varying experiences. Some are economists, some are physicians, some are statisticians. And everybody has a unique perspective on it; everybody has differing experiences that are really helpful in driving the question and the approach to answering the question. And so those two aspects of the job are the most fun.

DUTCHEN: It seems like that's how a lot of research progress is being made these days, right, is bringing in people who have different backgrounds and different approaches.

JENA: Yeah, I think so, and the other thing that I love about research is writing papers for journals and responding to reviewer comments.

[LAUGHTER]

JENA: I'm just joking. That we can all do without.

DUTCHEN: And what's the most challenging part?

[LAUGHTER]

JENA: That's the most challenging part.

DUTCHEN: What's the second most challenging part?

JENA: No, I think the challenging part is one that is to an extent modifiable, and that is when you're really optimistic about a question, it seems like there is promising initial evidence to support what you're doing, but it doesn't all fit. And ultimately the fragmentation in the findings is large enough that you can't come up with a coherent story, and you just have to drop it at that point. And that's a difficult thing to do, not only because you like the idea, you become attached to it, but also at some point you start to convince yourself that you know what the things that are consistent with the story, that those truths are more valid than all the things that are inconsistent.

And that's a challenge I think any researcher has to deal with, because at the end of the day what gets published is the best of what you've done. One never sees all the analyses that didn't work out, which is challenging. But I think the hardest part is letting go.

DUTCHEN: This is probably an exercise in frustration for you, and for people listening who want to know if these questions have answers, but what are some of the questions that you have either tried to look at in the past, or are wrestling with now, that don't seem to have enough evidence that you can really dig into what's going on?

JENA: That's a terrific question. Let me give an example from graduate school about a project that I thought was really interesting, but didn't pan out, and you're going to see why.

Well, many people will say that if a man grows up with two or three sisters, that he views women differently than if [he] grew up with two or three brothers. And the idea is that you maybe grow more sympathetic to women, or that the characteristics that we typically assign to women -- in terms of personality traits -- will spill over into the man. And so we looked at that.

We found that men with two sisters or two brothers are equally likely to be divorced, which you might think wouldn't be the case if men somehow treat women differently, or better, if they had two sisters; you might find lower rates of divorce. We didn't see that.

We also looked at another, even more extreme measure, which is rates of sexual assault. Again, the hypothesis being that if men treat women better because [they] had two sisters growing up, you would see lower rates of sexual assault. We didn't find any evidence of that.

So the conclusion I drew from that, was that if there is an effect of growing up with a female sibling, versus a male sibling, it certainly doesn't materialize in these really big measures that we looked at.

DUTCHEN: Is that not in itself a finding?

JENA: It could be. It's a terrific question. It all depends on what people think is the straw man -- I guess is the term that sometimes people use -- is if it were conventional wisdom that that were true, then I think that's a finding that people would be interested in. If it's not conventional wisdom, but it's something that you hear people once in a while say, it probably doesn't meet the threshold for trying to publish it.

And we're actually doing some related work right now which looks at using a lot of big data to try to understand whether or not adults who have male children versus female children have different life expectancies. So the kind of conventional wisdom may be that girls are more likely to take care of their parents than boys.

DUTCHEN: Or boys stress out their parents and send them to an early grave.

JENA: Or boys stress out their parents, exactly, yeah. And so we're looking at that now, and if you don't hear -- if the study isn't published, you'll know it didn't work.

DUTCHEN: Well, if it is published, I look forward to seeing what you find.

JENA: Oh, thank you.

DUTCHEN: Do you have any advice for people who might be considering thinking about things the way that you think about them?

JENA: Yeah, I think what I say to the residents -- and I'm not that far from residency, so it sounds a little bit premature for me to say this, but I'll say it anyway -- is that you see these things happening around you all the time, and it just might not occur to you that there is an interesting research question that is there. And I would say: Look around you, these things are all there. You just have to train your mind to think like that, and obviously, be interested in those sorts of questions; not everybody is.

DUTCHEN: What's the weirdest place you've picked up an idea from?

JENA: Oh. The weirdest place I picked up -- and I remember specifically I was at the University of Chicago, I was in my second year of my PhD, and like any good PhD student, I was on the internet. And so I used to look up articles on Yahoo News -- and a lot of people read New York Times, Washington Post, the Economist -- I actually like to read things like Yahoo News, because it just tells you what random people are thinking, and who knows what's published there, to be honest.

And in that article I saw something about Viagra and STDs. There was just some article that happened to be talking about Viagra and happened to be talking about STDs, but wasn't linking the two. And what I took from that was, "Is there a question here?" And if you started to look at the CDC data, what you would see was that at that time, STD rates were going up among the elderly, and it was around the same time that drugs like Viagra had been introduced. And so you can put two and two together and understand why those two might be linked.

And we used a large insurance data set and looked at people who use Viagra, and found that among those people, the rates of STDs went up shortly after use. And so that was the strangest place I saw something, Yahoo News.

DUTCHEN: So number one, keeping your eye out for questions. Number two, knowing how to formulate a good problem, like you said before. Number three, having enough evidence to really investigate the question. Number four, having thoroughness of mind and skill sets to really examine whether what you're seeing is association or causation. What else goes into all of this?

JENA: I couldn't have said it better myself. Wait, did you end on number four or number five?

DUTCHEN: I think that was four.

JENA: Four. I say number five is be prepared, and know when to cut projects early -- that's a challenging one, knowing when to let go.

DUTCHEN: When do you let go? I know you started to talk about this before.

JENA: Well, it also depends on what else is going on. If there's nothing else is going on, you can hold on for a -- this is almost like a relationship, it seems like -- when there's nothing else going on, you can hold on for a longer time, but when there's other competing projects, other competing responsibilities, I would let go faster. But whenever it's something in the data, either itself, or the analysis doesn't all line up as you want it to.

Let's say there's four sets of analyses that you think are critical to showing what you want to show. If two out of four of them aren't lining up, that's bad; three out of four is lining up, that's good; and so that's kind of a threshold I would use. If half the stuff that I want to show is not lining up properly, then I would throw it out.

And the other thing about letting go is when the data itself is perceived to be of poor quality, because when you look at a lot of different areas you have this problem of entering spaces where you may not be the expert, and there may be knowledge about certain databases that you don't know about. So some data that you might think would be terrific and high quality -- turns out that an expert in the field would tell you that it's horrible quality. And so when you find out that that's true, learning how to let go and say, you know what, let me not try to change this, it was a good idea, but that's what it was, it was a good idea.

DUTCHEN: Right, because I can imagine you can do some serious damage if you publish results that are based on faulty premises or data.

JENA: Yeah, exactly, yeah.

DUTCHEN: All right, what else haven't I asked you?

JENA: I think… My favorite color's blue. [LAUGHTER]

I think that's it.

DUTCHEN: All right! Well, thanks for giving us a glimpse inside your head.

JENA: Yeah, thank you, it was good.

DUTCHEN: I look forward into seeing what you've got next.

[MUSIC PLAYING]

DUTCHEN: And now for this month's abstract.

GROLEAU: Sometimes the names of structures we find within ourselves sound kind of poetic -- like the Cusp of Carabelli, and the islets of Langerhans, and the subject of today's abstract, Balbiani bodies.

Balbiani bodies are found in oocytes, which are immature egg cells. What they do is to keep mitochondria, proteins, and other important cell stuff in a tight package while the cell is dormant. It does this without a membrane, like the cell nucleus has. When the oocyte eventually matures into an egg, the package loosens, and its contents disperse within the cell.

In the lab of Timothy Mitchison here at Harvard Medical School, Elvan Boke and colleagues studied Balbiani bodies in frog oocytes. It turns out that frog oocytes are often studied to learn about human fertility.

Boke wanted to find out what kept the Balbiani bodies together, so she pulled the structures from a collection of oocytes -- not an easy feat -- and analyzed them. She found that the frogs' Balbiani bodies were mostly made of a protein called Xvelo. This was the first reported instance of a cell using a protein to create a compartment. That's pretty cool.

Xvelo clumped together to form a network of amyloid fibers. Amyloids are often associated with neurodegenerative diseases like ALS and Alzheimer's, so they don't have the best reputation. Here, though, they perform a necessary function.

In addition to learning more about Balbiani bodies themselves, Boke hopes researchers will learn what causes the amyloid structures to break apart when the oocyte matures -- and that could lead to treatments for those amyloid-related neurodegenerative diseases.

[MUSIC PLAYING]

DUTCHEN: This podcast is a production of Harvard Medical School's Office of Communications. Thank you for listening.

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END OF INTERVIEW