

Mark Masselli (00:04)

If you're 65 years of age, you have about one in 20 chance of developing the most common form of Alzheimer's disease in the next decade. It's a sobering statistic. How strong is the current research into the cause of Alzheimer's disease?

Charles Piller (00:20)

There has not been often rigorous analysis of scientific images. And so what you have are a multitude of images, not just in Alzheimer's disease, but in many other areas that have slipped through that have not been well, well examined, and that are in fact falsified or appear to be falsified and have not gotten the rigorous look that they should be getting in order to reexamine whether the pre the, the experiments themselves are worth publishing.

Margaret Flinter (00:52)

Charles Pillar is an investigative journalist for Science Magazine, and he's the author of the new book, *doctored Fraud, arrogance and Tragedy in the Quest to Cure Alzheimer's*.

Charles (01:02)

Personally, I think that research should continue into amyloid proteins and what, what impact they might have, but that research should and is being broadened to other ideas about the causes of Alzheimer's. And a couple that I am extremely interested in, and I think, are going to be fascinating to watch in, in the coming years. One is the possible impact of GLP one inhibitors. These are the seemingly miraculous drugs that are used for obesity and diabetes, and now are being examined for lots of other ailments.

Margaret (01:37)

This is *Conversations on Healthcare*.

Mark (01:50)

Well, Charles, welcome to *Conversations on Healthcare*. Thanks so much for having me. I, I appreciate being here. Yeah. You know, your book covers a really complex issue. I'm wondering if we can start by asking you to explain the allegations at the center of your investigation.

Charles (02:07)

Sure. So what I try to do in the book is to examine some fundamental questions about disappointments, basically in the progress towards finding remedies and eventually a cure for Alzheimer's disease. And as I think many listeners would know, there has been a period of great disappointment associated with Alzheimer's for the last 30 plus years. There's been a dominant way of looking at the disease called the amyloid hypothesis. And even though there are a couple drugs now on the market associated with combating the disease that are directly tied to that hypothesis, their benefits have been at best, extremely minimal, and some would say even imperceptible to patients. And yet they also pose some very, severe risks for a minority of patients who take the drugs. So what I tried to do is look really underneath all of that and to look deeply at the possibility that the research perhaps has gone astray in a variety of ways, including both a kind of group think associated with that hypothesis, and also, manipulation of some of the research that has skewed scientific thinking in the field.

Margaret (03:24)

Well, we, understand that investigations are continuing, and, and several of the key people involved in those investigations have denied any knowledge of wrongdoing, but publications have withdrawn some research papers that have been submitted, by scientists because of issues that you, identified and yet a mixed reaction to all of this from the scientific community. I'm sure it's very complicated, but what's the range of opinions that are coming forward?

Charles (03:51)

Sure. Well, let me, if I may, give you a couple of examples that I think reflect some of the concerns and also the conflicts within the scientific community associated with my reporting and the investigations that I've done. So what kicked off this book and my years of research into this kind, this range of issues was, an investigation that I did with the collaboration of forensic image experts into work done by a team of scientists at the University of Minnesota. The lead scientists were this guy, Silvan Lne, who was at the time a postdoc in the lab of a very prominent Alzheimer's scientist name of Karen Ash at the University of Minnesota. And their study was very, very important in, undergirding and supporting this idea that the amyloid hypothesis of Alzheimer's disease was, essentially the central idea behind how to, find remedies and eventual cures for Alzheimer's. And maybe just, if I could just digress mm-hmm. Very slightly to explain what that is specifically. Yeah. The amyloid hypothesis is this idea that these certain kinds of proteins that accumulate in the brain called amyloid proteins cause a cascade

of biochemical effects that eventually lead to Alzheimer's dementia. And this idea has been prevalent in the field and has absorbed the lion's share of, you might say, mind's share among scientists and also the lion's share of funding for decades. And it's done this in part because it was a very logical, it is a very logical way of thinking of it. You, you have this accumulation of proteins. You have some genetic association between the amyloid accumulation and Alzheimer's dementia. So it's, it's something that scientists thought made a lot of sense, but unfortunately, the remedies developed based on it failed time after time after time. And so you had the ability to remove these amyloid proteins from the brain, but not to arrest or reverse the symptoms of Alzheimer's disease. Really what we're all after is finding remedies to this terrible disease. And so in 2006, this experiment, this important experiment took place at the University of Minnesota that seemed to validate the amyloid hypothesis in a, in a new and important way. It, she seemed to show a direct cause effect relationship between a certain type of amyloid protein and a cognitive decline or memory loss in rats. And so it was an animal experiment, but it was such a strong validation that, people in the field really felt that it had been a shot in the arm for validating this way of looking at it and really reinvigorated both funding and the idea of how to attack Alzheimer's disease and the way scientists were thinking in the field. And it made it so that this idea was kind of, became renewed as a way of looking at the, the field. So, okay, fast forward to 2022, working in collaboration with a particular scientist at Vanderbilt University, Matthew Schrag, who has, both image integrity assessment tools in his, his toolkit, and also is himself a neurologist who treats Alzheimer's patients and a neuroscientist who runs his own lab to study the disease. He, found what appeared to be really central flaws in this experiment involving a parent image doctoring. And when I wrote an article about this in Science magazine exposing this range of apparent image doctoring in this very important study, the response was immediate and dramatic from the scientific community. So finally, if you'll forgive me, I'm getting back to your direct question. How has the scientific community been responding? And in this case, there were really two kinds of responses. Some scientists said, this is an opportunity for us to take a good hard look in the mirror and ask ourselves, do we need to broaden our horizons and give more emphasis to other ways of looking at the disease that might open up new horizons for understanding and treating Alzheimer's disease? Have we put too much faith in one way of looking at the disease? Others said, we believe that this is terrible, that there was apparent image manipulation associated with this study, but it doesn't mean anything. We're completely committed to the amyloid hypothesis and all, and many of them would say things like, we knew all along that this study was questionable. But it was very ironic because those same scientists, many of them leaders in the field had cited this study over and over and over for many years as a one element of how they supported their own ideas in the field, how they believed and justified their own emphasis on this same hypothesis. So I would say that was at best, ironic and at most a bit hypocritical. So that was the response initially.

Margaret (09:29)

Well, Charles, I wonder if I can, having gone broad on that, just curiosity, maybe go a little bit deep, image doctoring. I think our listeners are probably trying to sort of figure out where the doctoring comes in. So let's just call it image manipulation or image, distortion maybe, that we're, talking about here. In, in your review, did you, find that there's a standard process for layers of review, generally speaking, I would assume there's the primary reviewer and maybe a secondary or even a tertiary reviewer before you would draw conclusions on something like this. Did you come away from it feeling like, yeah, there's good processes in place, so we don't know how this might have happened? Or did you come away from it thinking, gosh, maybe we don't have the level of secondary and tertiary few that lay people or even, you know, not lay people would think would be in place?

Charles (10:24)

Sure. Well, let me start by telling you what my process is, and then I can put that into the context of what journals and regulators and funders do, because it's very different. So when I encounter allegations of inappropriate image doctoring on the part of Alzheimer's scientists, I put it through a very rigorous set of, assessments that involve vetting the concerns very thoroughly. So the first way that I vet it is that I make sure that the analysis that is, is done has been done associated with my work. And that's, done usually by very expert forensic image experts, is vetted by others in that field. So in other words, I take their results of their examination of scientific images that apparently were doctored in ways to support improperly the, the hypothesis behind particular experiments. And I ask other forensic image experts, are these analyses well-founded and well conducted? And if it passes that test, then I go to experts in the field of Alzheimer's research. So these are world-class experts who understand not just whether these images might be falsified, but also the meaningfulness of it. Are these important images? Are these images that fundamentally change the interpretation of an experiment mm-hmm. That might have influenced the field in one direction or another? And if it passes both of those tests, then I go and I can write about it with confidence. Now, let's contrast that for a second with what has historically gone on at scholarly journals and at the, the, some of the major funders, there has not been often rigorous analysis of scientific images. And so what you have are a multitude of images, not

just in Alzheimer's disease, but in many other areas that have slipped through that have not been well, well examined, and that are in fact falsified or appear to be falsified and have not gotten the rigorous look that they should be getting in order to reexamine whether the pre the, this experiments themselves are worth publishing. Now, let me just give you an example of, something that I think we should all regard as a cautionary tale for the field of Alzheimer's research and more generally in science. So last fall, I wrote in the pages of Science magazine, an article about an investigator by the name of Eliza Mosley, who was until recently the head of the Division of Neuroscience of the National Institutes of Health. And as such, he had an instrumental role in guiding what research became funded and became important in the thinking of the scientific community regarding Alzheimer's and other neurological conditions. And, because he was so important, he, he, I should say that he attained that job because he was a person who for decades had been a very influential researcher at the University of California San Diego. And his work was among the most cited in the scientific literature, literally for decades now, what my story showed was that in more than a hundred of his scholarly papers, there were strong evidence of improper image manipulation or reuse of images. These are studies that affected drug development and affected scientific thinking in profound ways. And when my story came out last fall, on the day it came out, the NIH synchronized its own announcement, that he was no longer gonna be the head of that division. And this was on the basis of them examining two studies, just two out of the multitude of studies he wrote. And compared to the more than a hundred studies that were evaluated in the dossier that was created as part of the work, that I was doing for that article, he was then found to have been engaging in misconduct on just two studies. And I, I wanna leave you with this little anecdote with, with a, a very sobering, kind of capstone to it, which is that when I asked the National Institutes of Health if they had had a practice of checking their top leadership for possible image manipulation in their studies prior to their being hired to these important jobs, the agency said no, and they didn't think that it would be beneficial to help with the conduct of research at the agency. This, to me, was a, a sign of, complacency and arrogance that was stunning to me. It, it shows that we need more vigilance, more, really just a better way of looking at these issues by these leaders and these agencies, and to understand that these are serious matters that can affect the way in which Alzheimer's research and other neuroscience research is conducted and how it affects the American public. So that sort of example shows me that we really do need reform. We need, we need, there to be a really invigorating way of changing the approach of these, funding agencies. Similarly, at the scientific journals, there has been improvement. And I work, for the Journal of Science, and I'm happy to report that science and several other journals, many of the leading journals have begun to take this issue more seriously and are beginning to approach this as a fundamental part of their due diligence process, which needs help and needs reinvigoration as well.

Mark (16:35)

Well, That, that's very interesting. Charles. I want to pick up on, a couple of things. So maybe there's two parts to this question. One, you're sort of talking about world class experts, and then we were talking about America's research focus. It's, it's not an American problem, Alzheimer's, it's a, it's a global problem. So are you finding the amyloid mafia internationally, to exist in, the EU and other large, places where funding comes out of? And then what are you seeing on the horizon of alternative research into Alzheimer's, that our listeners might be, interested in hearing about, seeing, knowing that the current strategy has not worked so successfully?

Charles (17:22)

Thank you for that question. I think it's a very important one. First of all, I wanna make it clear that, even though I have written skeptically about the amyloid hypothesis and that many other, many scientists share the view that there's been an overemphasis on the hypothesis, even the most strident skeptics of the amyloid hypothesis believe that amyloid proteins and the processes that they may be involved in in the brain have something to do with Alzheimer's disease. The question is really not whether they have something to do, but whether they are the linchpin of Alzheimer's disease, whether in effect they have everything to do with the disease. And so, personally, I think that research should continue into amyloid proteins and what, what impact they might have. But that research should and is being broadened to other ideas about the causes of Alzheimer's in a couple that I am extremely interested in, and I think, are going to be fascinating to watch in, in the coming years. One is the possible impact of GLP one inhibitors. These are the seemingly miraculous drugs that are used for obesity and diabetes, and now are being examined for lots of other ailments and drugs like Wegovy and, and others that are already on the market are thought to possibly have an influence on Alzheimer's disease as well. And clinical trials, large scale phase three trials. And these are the normally the last set of trials prior to possible approval for, use in the United States by the Food and Drug Administration. There are currently phase three trials going on with GLP one inhibitors that as early as next year, we may know some sort of conclusion about whether they might be beneficial for slowing or arresting the effects, the cognitive decline, I should say, of Alzheimer's disease. So that's what I'm really keeping my eye on. Another is the so-called infection hypothesis of Alzheimer's disease. This holds that latent infections in the brain, including with such, viruses such as the herpes virus, which listeners may recall, causes cold sores that resolve. And then, they may not know that it can, hang

out in some organs of the body, including the brain for up to decades, and are thought possibly to influence dementia in Alzheimer's dementia in people. And there are studies, clinical studies going on right now to examine the possible benefit of treating those latent viruses. Mm-hmm. So those are two very hopeful things. Mm-hmm. I, I think I should also say that people can have a very kind of despondency about Alzheimer's disease, a sense of hopelessness because it's such a, a terrible ailment that steals our memories and our ability to function in everyday life. And ultimately even for unlucky people who advanced Alzheimer's, our sense of self, the kind of elements of our, our personhood that, can be so devastating to the people with Alzheimer's and their loved ones. But there is something that people should remember that we have agency associated with this disease, that things like watching your blood pressure mm-hmm. Your cholesterol levels, eating a healthful diet, exercising the, there's no supplement or lifestyle habit that is cure or absolute preventive to Alzheimer's disease. But these are all things that we have some degree of control over. And that living our best lives is also a way of helping to ensure that the worst symptoms of Alzheimer's disease, that if we're unlucky to eventually get the disease, can be forestalled or tempered by having these kinds of, really deliberate habits that can be something that would benefit us in many ways as well.

Margaret (21:34)

Charles, we're living in a time of great mistrust of science and one review of your book states that we're left wondering if any research can really be trusted. How do you answer that question?

Charles (21:46)

Sure. This is a question that I welcome because, I'm an investigative reporter and I've written critically of misconduct in science many times, not even just in Alzheimer's research, but let me say unequivocally that while there is misconduct in Alzheimer's research, a v it's a very small percentage of the overall research that's done. Just like any walk of life or any scientific field, a small number of scientists in this field engage in misconduct, cut corners, or even commit fraud in order to advance or to make money. And while this is reprehensible, it does not represent the vast bulk of scientists in the field. At times. People may misunderstand and extrapolate some doctored studies, some misconduct to the idea that all of this research is suspect, or all of this research cannot be trusted. And I would just object to that unequivocally and say that I think an enormous amount of incredibly good work continues to be done in the field.

Mark (22:52)

And, And in fact, you're a founding member of the Center for Public Integrity served on its board, as its chair, I believe. I'm wondering if you can tell us about the center and its investigations into our healthcare system through the years. Tell us a little more about what's been exposed.

Charles (23:10)

Well, I mean, unfortunately the center has stopped, operating recently. It has historically, it was a group that was dedicated to, basically looking at, not just misconduct, but also service in government and in industry, and finding out what elements of our programs and our processes are not to be trusted and should be reexamined. And, I can't, I'm not the best spokesperson for, the entire legacy of that group. But what I can say is that investigative reporting overall is, you know, in a kind of, way in which journalism is trying to play a positive role in society, and unfortunately has suffered from funding cutbacks and in inability to get the degree of support that we need in order to do a robust job. Let me just, say that I'm very grateful to Science Magazine for, supporting me to do this very difficult and expensive work, time consuming work, and the many nonprofit organizations have started to fill the gap when major news organizations have been unable to fund as much investigative reporting as they'd like to.

Mark (24:29)

And, and maybe our group has not heard of, our listeners may not have heard of Science Magazine. Tell us a little bit about, where they can get it and a little bit about as genesis as well.

Charles (24:39)

Sure. Science Magazine is one of the preeminent scholarly journals in the world, and it publishes a wide range of si basic scientific research. And, along with the journal, nature is regarded as one of the two most important general interest scientific journals in the world. But the part of the book that I work for and, and the book is a term of art in journalism for what a magazine is, and it's the journalism side of the magazine. And so I don't get involved in basic research, of course, I'm not a scientist, but what I write about is, important issues in science that deserve journalistic coverage and that would be of wider interest to the community. The public is at a, at large, not just the scientific community. Science itself though, has, is a quite influential publication. It's published by the American Association for the Advancement of Science, and it's a nonprofit, and so it's a

membership organization and it, is a organization that exists to further the development of scientific research. That's in part why it's so important to me that people interpret my journalism as something that is very supportive of science, also very critical of science done poorly or improperly.

Margaret (26:04)

Well, Charles, I'm really glad you chose to, end on that message. I think it's an important one for our listeners while they also, absorb the other, valuable information that you've provided our listeners with today. So thank you Charles, for joining us, and thanks for our audience for being here. Just a reminder, be sure to subscribe to our videos on YouTube and find us on Facebook and X. You can also share your thoughts and your comments about this program. Thank you and be well.

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