

## Fixing Healthcare Podcast Transcript

### Dr. Siddhartha Mukherjee

- Jeremy Corr: Hello, and welcome to season four of the Fixing Healthcare podcast, I'm one of your hosts Jeremy Corr. I'm also the host of the popular New Books in Medicine podcast and CEO of Executive Podcast Solutions. With me is Dr. Robert Pearl. For 18 years, Robert was the CEO of the Permanente Group, the nation's largest physician group. He is currently a Forbes contributor, a professor at both the Stanford University School of Medicine and Business, and author of the bestselling book, "Mistreated: Why We Think We're Getting Good Health Care-- and Why We're Usually Wrong."
- Robert Pearl: Hello, everyone and welcome to a new season of Fixing Healthcare, which will focus on big ideas and the people behind them. We also invite you to check out our new weekly show, Coronavirus: The Truth, available through Apple Podcasts, delivering informed commentary, helpful content and reporting from only the most credible sources. On last week's episode, we outlined a plan to reopen the economy, we explained the \$2.2 trillion CARES Act, and we dispelled some of the myths currently competing with the scientific facts. One more note before we dive into this week's episode, throughout last season, we shared the results of our second-ever Fixing Healthcare Survey and encouraged listeners to share their opinions. You can check out the final results of that survey on my website, robertpearlmd.com, and while you're there, you can subscribe to Monthly Musings, my free newsletter, offering the latest news and opinion from the world of healthcare.
- Jeremy Corr: Our guest today on Fixing Healthcare is Dr. Siddhartha Mukherjee. He's a physician, virologist, oncologist, and author of the 2011 Pulitzer Prize-winning book, "The Emperor of All Maladies: A Biography of Cancer." In 2016, he published the New York Times bestseller, "The Gene: An Intimate History." This month working in conjunction with Dr. Mukherjee, Ken Burns released a two-part PBS documentary based on this material and theme.
- Robert Pearl: Hi, Sid, how are you doing?
- Siddhartha Mukh...: Very good, thank you.
- Robert Pearl: It's great to have you on our podcast, Fixing Healthcare. This is the fourth season, it's dedicated to big ideas, and you've had a huge number of them across your career. Let's start with a superb article that you just published in The New Yorker magazine, titled, "How Does the Corona Virus Behave Inside a Patient?" Can you tell listeners, what's the underlying thesis?
- Siddhartha Mukh...: Well, the underlying thesis is rather simple. When a pandemic happens, like the one that we're in the middle of, the first instinct is to measure the spread of virus across populations. How many people are infected? Who's symptomatic? Who's asymptomatic? That's a very crude measure. The thesis is that, now as

we move into the mid-phase of the pandemic and we're starting to treat people, triage people, figure out who's sick, how to deal with people, and figure out who's likely to get bad disease versus mild and moderate disease, there is no good disease, who's asymptomatic, who's symptomatic, we need to start measuring the viral loads within individuals. We need to standardize them, we need to use them for clinical trials. We need to figure out whether high-dose exposure to the virus through respiratory sputum and symptoms and saliva, make the disease likely to become worse.

Siddhartha Mukh...: In other words, there's a dose relationship with the severity of the disease, because each of these leads to a slightly different policy implication. So, just to give you a couple of them. One of them is, if we could figure out which patients are likely to do worse than others, based on how much viral load they have, then we could triage patients much, much more effectively than we have been.

Siddhartha Mukh...: If we could figure out that, in fact, that the amount of virus exposure that you get is related to the severity of disease that you experience, and that is true for many other respiratory viruses including SARS itself, not SARS-CoV-2 but the original SARS, then we could figure out that we need different kinds of protective equipment depending on whether you're getting very large acute exposure as healthcare workers on the frontline are exposed to, versus whether you're getting low-dose chronic exposure, like you might get at a grocery store or at a bodega or in the subway. So, each of these has deep policy implications and how we manage the next steps in this pandemic in the United States and elsewhere in the world.

Robert Pearl: Is there any evidence from other viral infections in the past that this viral load might be an important factor?

Siddhartha Mukh...: I would say there's a mountain of evidence. A few exceptions aside, most respiratory viruses have a dose-infectivity relationship, and they have a dose-severity relationship. And let me explain what both those are. The dose-infectivity relationship means that the chances of you getting infected with the virus depends on the amount of dose that you get. There is evidence from influenza, there is evidence from measles, that the amount of dose that you get relates to the chances of you getting infected. Low-dose virus is often dissipated, high-dose virus is very likely to cause an infection. Secondly, but more importantly, there's a relationship between dose and severity, we know less about this in coronaviruses. We know more about this in other viruses, such as influenza and measles, that there's evidence that suggests that if you get a very high dose of virus, you are likely to suffer or more likely to get an infection that is more severe.

Siddhartha Mukh...: And as an immunologist, I was trained as a viral immunologist, part of my lab still works on viruses, there is evidence to suggest why this might be the case. And that's because a virus doesn't... Your body is not an empty pot or a vacuum. A virus is not entering a vacuum, it is entering a body, which is prepped for battle. We as human organisms have been battling viruses and microbes for

millennia, and our bodies have developed responses to these viruses and these microbes, and these defenses start kicking in as soon as the first viral particles reach our oropharynx or nasopharynx, or any parts of our body. So, you really should imagine this not as a plus-minus phenomenon but as something dynamic. Your body mounts an immune reaction, that immune reaction reaches an equilibrium with the virus. It's like a seesaw. And if there's lots of virus on one end and your immune system is not prepared on the other end, the virus wins and takes over, and starts replicating and your immune system is unable to combat it.

Siddhartha Mukh...: On the other hand, if your immune system is prepped, if it meets a low-dose of virus, it has the capacity to handle it, it cannot get overwhelmed and it can subdue the virus before the virus takes over. In the 19th century, the Russian immunologist, Ilya Mechnikov, who was one of the founders of immunology, described this as a perpetual struggle, he called it "Kampf." And every time you encounter a virus, it's a Kampf, it's a battle. And our job as doctors is to tip the equilibrium towards the host, towards the human, and tip the equilibrium away from the virus. And there are various ways one can do this. Vaccination is essentially one way that we tip the equilibrium towards the host, right? We have pre-made immunity or pre-created immunity against a virus or a microbe. Vaccination is also not a plus-minus phenomenon, all you're doing is tipping the equilibrium towards the virus.

Siddhartha Mukh...: Another strategy is to limit the amount, the dose, or the exposure to the virus, which is by wearing protective equipment. In the case of healthcare workers who are getting very high loads of virus in their body, that means wearing protective equipment that can really filter the virus and ensure that you're protected from high dose virus, because you're meeting people who are symptomatic or acutely shedding vast numbers of viral particles. In the case of non-healthcare workers, there is evidence to suggest that a simple mask, such as a surgical mask or even a piece of cloth, used appropriately, along with gloves and hygiene, and hand hygiene, and social isolation measures will help in preventing you from acquiring a virus.

Siddhartha Mukh...: So, I think that there's really a lot of evidence that suggests that the load of virus that you get and how you deal with the virus, and the viral load that you carry once you're infected in the body can be used as thoughtful guidelines in managing an infection once you are infected. And that's what I mean. We've been measuring the virus across populations, we need to start measuring the virus within populations, within people as it spreads through communities.

Robert Pearl: Can you explain, Sid, for the listeners, the difference between testing for the disease and doing antibody measurements to determine who's had the disease?

Siddhartha Mukh...: Yes. So, most viral infections go through two phases. The first phase is, when you get acutely infected by the virus. And with SARS-CoV-2, we know that when you get acutely infected with the virus, some people are asymptomatic, and some people have symptoms, they develop flu-like symptoms, there's a whole

list of symptoms that you can develop as a response to SARS-CoV-2. Your immune system starts mounting a response to it. It starts creating antibodies, B-cells and then, potentially T-cells and other immune cells that begin to fight the virus. Eventually, if you defeat the virus, and if the virus now has been mostly destroyed in your body, your antibodies begin to show that response. So, you can divide the world, as it were, into three broad groups.

Siddhartha Mukh...: One group would be people who are naive, they would be people who have no virus in their nasal swabs, or oral swabs, or respiratory secretions, this can be tested using a test. But they also don't have any antibody because they haven't seen the virus. Their bodies have not seen the virus. So, that's the naive population. Then the second population is the so called active disease population, people who are actually carrying the virus, shedding the virus, and are very infected and infective. They can possibly infect other people. So, those are actual viral patients. In their bodies, you can see virus, you may be able to see first signs of the antibody developing. The antibodies that come, we can make distinctions between antibodies that are produced initially as a result of the infection and antibodies that are produced once the infection has subsided. It takes about a month usually, to switch from the first class of antibodies to the second class of antibodies.

Siddhartha Mukh...: So, that's the second population. The second population is people who have active disease. They have virus in their nasal swabs, they have virus in their oral swabs. And they may be showing the early signs of antibodies. And then, there's a third population, the so called post-immune population. These are people who've encountered the virus, they've had the disease, they may be asymptomatic or symptomatic, but they've cleared the virus. There's no more virus left in their oral swabs or nasal swabs, but now they have antibodies against the virus, they have become immune to future infections by this virus. So, again to recapitulate, you can divide the world into the naive, the actively infected, and the post-immune. And each of these three populations has different risks, of course.

Siddhartha Mukh...: A person who is naive has the risk of getting the virus and then, the consequences of what the virus might be. They need to protect themselves. If you're vulnerable, if you're concerned, you need to protect yourself, and there are ways to protect yourself including, as I said, social distancing, hand hygiene, quarantining, isolation and, finally, wearing a mask to protect yourself from potential respiratory fomites or cough droplets that someone else might spill on you. This is the naive population. The second population is a population that's actively infected. This is the person who has the virus in their nasal or oral swabs, are shedding. It would be good to know how much they have, because we could give them some advice about the degree of isolation that they need to have. But this population needs to be self-quarantined or be in a hospital if you're sick. These people might be the people that we might want to enroll in clinical trials, to figure out if we can have a good antiviral drug.

Siddhartha Mukh...: This is a very vulnerable population, we need to figure out who these are, isolate them, quarantine them, hopefully, be able to test their contacts, track their contacts and place them in quarantine so that they don't shed or spread the virus. And finally, there is a population... And of course, if these people were to go out for whatever reason, they must wear masks, especially high-grade masks, because they are likely to spread the virus to other people. They need to practice a lot of hygiene and a lot of self-discipline to ensure that they don't infect others. Because as we know, the infectivity of this virus is more than typical viruses, one person infects, we think on the order of two to three people without the appropriate measures, without social distancing, without gloves, without masks, and so forth.

Siddhartha Mukh...: The final population is the post immune population. The post immune population is actually a population that is... Knock on wood, if they have had a mild version of the disease, and they've survived, they have developed antibodies, and we know that those antibodies are protective. The evidence that they can get reinfected by the virus is very low. Mostly, that is likely because of false testing. These people are actually safe. And in countries such as Great Britain and Germany, there are now some thoughts about whether those people can be released to go back to work.

Robert Pearl: One of my concerns is that people talk about, in quotes, beating the virus, implying that if they socially distance in order to flatten the curve and not overwhelm the hospitals now, that they will then be able to avoid ever getting the infection. Because a vaccine is more than a year away, how will our nation manage to expose the 180 million people needed beyond the 20 million that might have developed it during this most initial phase?

Siddhartha Mukh...: Well, so, I think the appropriate thing to do... And I've certainly been writing a lot about this and being on social media about this, the appropriate thing to do is that, hopefully, once the acute phase of this pandemic dies down, that we lift the restrictions on the acute phase in a gradual and thoughtful manner. In other words, the people who are naive, so let's say that's 30%, 50%, 70% of the population, we don't know, we need to find that number out, that is a number we need to know, because that's a data point that we need to establish. And the only way to establish that data point is to do random testing for both antibody and for virus in people. In other words, if you only test symptomatic people in hospitals, you're going to get a biased sample, because of course, they're sick and that's why they're coming to get tested.

Siddhartha Mukh...: What you need to do is to go to communities at some point in time and run relatively small numbers... And we're not talking about massive numbers, but relatively small numbers of people, and test and figure out, how many people are actually infected? And how many people are post-immune? And how many people are naive? The three categories that I talked about right up front. Once we have those numbers, let's say in June or in May, we'll have a sense of what the face or the demographics of this epidemic look like. Once we have those numbers, we can make some important decisions about how to lift the

lockdowns and quarantines and warnings, et cetera. If it turns out that most of the population is naive, then two or three things need to happen. We need to continue social distancing and we need to continue wearing masks for people who are naive, because that's the only thing that will protect them from future infections.

Siddhartha Mukh...: If it turns out, of course, that 90%... I hope it doesn't. But 90% of the people have been exposed to the virus then we will continue the same kind of measures but of course, the chances of having a full relapse again of the pandemic are lower because the immunity will last longer. The most important thing to do and the reason that we're saying that we should be distancing during this time is to buy us time. And I'm going to repeat that again and again, in this podcast, we need to buy time. We need to buy time so that the hospitals are not overwhelmed and the healthcare workers can be adequately protected and adequately supplied with the equipment that they need to deal with the sickest patients. The healthcare workers themselves need high-grade masks, not cloth masks, not simple masks, but high-grade masks that will protect them from the amount of viral exposure that they're getting. And they need gowns, they need gloves, they need ventilators, and there's a limit to what that number is.

Siddhartha Mukh...: So, by flattening the curve, what we're really doing is allowing healthcare workers to do their job and protecting people's lives, as opposed to overwhelming the hospital systems in ways that the hospital systems will ultimately break. That's one. And number two is, the other reason to buy time is that there are many, many medicines being tested, including antibodies, manmade antibodies, including small molecule drugs, et cetera, which may work and will hopefully work against critically ill or even moderately ill patients with virus. Once we have those drugs, all of a sudden, the capacity of a healthcare worker or the hospital system to be able to deal with all of this will change, because we will be able to treat this like an acute viral infection, which has a medicine, you go to the hospital, you take the medicine and your viral shedding becomes lower and you become better. And so, the entire tone of this economy and of the pandemic will change because we will have potential solutions.

Siddhartha Mukh...: These don't come instantly, they take time to be made. In order to do that, we need to let medicine do its work. It takes time, it takes months before this can be done. And of course, as you said, the final phase, which will probably take about 12 to 16 months, is to find the vaccine, and when the vaccine arrives, hopefully, we'll be able to protect those who are naive and who have not been exposed, so that they don't get infected.

Siddhartha Mukh...: So, you should really think of this as, I would say, nothing else than a public service. Your job is to flatten the curve to, number one, protect yourself. Number two, protect the overwhelmed medical worker who would not be able to otherwise do his job. Protect the economy, so that we can resume it as soon as we can possibly resume it. And most importantly, to buy time to solve the

medical crisis, because unless we solve the medical crisis, we're not going to solve the economic crisis.

Robert Pearl: As a physician, I'm very aware of what you're describing. And there's no question in my mind the right thing to do right now is social distancing. I'm trying to ask, though, a different question. So, I follow the literature very closely on chloroquine, on antibodies in plasma, et cetera, I'm not seeing a lot of evidence it's going to work. You're right, it could work, but I'm not seeing the evidence yet.

Siddhartha Mukh...: So, the chloroquine is a separate story, and it's very unlikely to be... The evidence is very mild. The antibodies are quite something else, because we know a couple of things. One is that the few patients who have been treated with post convalescent plasma have actually had recovery, which argues that antibodies made by humans can in fact, protect you from the virus. We have to find those antibodies and make them en mass and give them to people who are ill. There's a paper in Science Today which actually describes the crystal structure of an antibody bound to not SARS-CoV-2, pardon me, but SARS it's close cousin, and shows exactly where the antibody binds. So, we know, potentially, where the protective so called area of the virus is, where you could drive an antibody response to it.

Siddhartha Mukh...: Antibodies take time to make it, they're not like aspirin, they're not like penicillin. They take time to make because they are biologics, they're protein drugs. But I'm confident that there are going to be antibodies that will decrease the effects of this severe disease in patients, they will just take time to make. Chloroquine is a completely different story. Chloroquine is a repurposed drug, it has probably some mild effect against the entry of the virus and the evidence that it changes the course of disease is pretty mild.

Jeremy Corr: In terms of the COVID-19 and novel coronavirus, we are... Like you and Robbie discussed, my question is... And I know Donald Trump and others have talked about this, is, at what point is the cure worse than the disease in terms of slowing the economy, closing it off for so long, people losing jobs, depression, suicide, and all of the different social determinant of health issues that go along with that? What do you think is the best way to handle that? I mean, I know there's no right answer, but what do you think the best way to balance those both out is?

Siddhartha Mukh...: Well, I think I am one in the camp that believes that without appropriate medical therapy, we do not get economic emancipation. People will be frightened, people will be infected, people will be dead. So, I think we need to get the medicines first. The way to get the medicines first, as I told you, is to phase in and phase out. I would give the administration a D- grade in the preparation for this pandemic. We knew about this in December, in a globalized world, it is a travesty that medical workers in the frontline, in the wealthiest nation of the world, don't have the equipment that they need to handle patients. It is a travesty.

Siddhartha Mukh...: So, my entreaty, my plea, to the administration would be that, if we want to open the economy again, and I believe it's a good thing, I would like to go back to work, I would like my lab to go back to work, it would be a good thing to not be cavalier about opening the economy. And to encourage as fast as possible, the use of safety for the medical personnel, the use of safety for the public, using widespread testing not only with the antibody, but also with the oral swabs to figure out who is naive, who is immune, and who is shedding virus. And finally, when we lift the phase, to lift it in thoughtful ways, so that we don't re-expose the country to a pandemic that's in the middle of the worst ravages.

Robert Pearl: So, Sid, you're about to release with Ken Burns a movie based on your New York Times bestseller, "The Gene," can you tell listeners about it?

Siddhartha Mukh...: Yes, I mean, the movie was filmed before the pandemic, so we don't have very much about the COVID-19 pandemic in it. The movie is an adaptation of my book, "The Gene: An Intimate History." I should tell you, it's been an incredible pleasure working with Ken Burns on this. The movie is not the book, they're different beasts. The movie follows many more case histories, the book is more historical. It has a much wider arc of history. The movie follows more recent developments. It opens with the staggering footage from the first meeting, when a Chinese researcher climbs nervously on the stage and describes himself performing experiments that lead to the birth of two so called genetically designed babies. He has gene edited, he has edited the genes of two babies who have now been born, and the scientific community is stunned and horrified, because it has not really been told about these experiments.

Siddhartha Mukh...: So, the movie covers some history, a lot of case histories of individuals. It has intense and incredible footage about the language of genes, and how we can learn about human genomics. I should say two things about it. One is that, although as I said, the movie was finished long before this epidemic, it is essential to learn the vocabulary of genes and genetics, in order to understand what's going on in the world today. The virus is a piece of genetic material that is packaged in a code that infect cells and parasitizes the genetic operators of our own cells and uses it to replicates itself. The virus genome, the genetic material of the virus was sequenced in record time, because over the last 10 years, we've learned to do this on the human genome. The way we track the epidemic, the oral swab, the way we track the viral loads in individual patients, the way we make antibodies against the virus for therapeutic use, all of these depend on technologies that are covered in the film.

Siddhartha Mukh...: So, the film is extraordinarily relevant. It's on PBS on April 7 and April 14, and it will arm you with the vocabulary and with the necessary data that one needs if you want to participate in this conversation, about how to arm ourselves against COVID-19. Without the century of genetics that preceded this pandemic, we would be armless against COVID-19, just as we were armless against the Spanish Flu of 1918. It is almost precisely, 100 years since the Spanish flu. We have a host of techniques to test and to follow the course of the virus as it moves to

the human population, and to develop new therapeutics for it. All of these depend on genetic testing and on genetic technologies.

Siddhartha Mukh...: If we have a vaccine against SARS-CoV-2, it will likely depend on recombinant DNA technology, the very technologies that were used to first make insulin and other drugs such as Herceptin, which are very well covered in the film. So, I would encourage people to watch the film not only to educate yourself about what is going on in the world in terms of genetics, the ethical quandaries that it raises, the personal quandaries that it raises, but also if you're interested in understanding... How to understand the vocabulary around this particular pandemic, all of these would be reasons to watch the film and plus, I'm sorry to say, you're going to be trapped at home so you might as well educate yourself.

Robert Pearl: It's remarkable how much information is encoded inside those double stranded DNAs in our body, and it's amazing how much information is encoded onto a single silicon wafer. How do you compare these two technologies, one natural, obviously, and one man-made?

Siddhartha Mukh...: Well, I think that they're both mechanisms of information. And in the film, I talk about the idea that, you cannot understand computers, you can't understand computing until you understand how information is coded in bits and bytes. You can't understand the material world unless you understand an atom. You cannot understand how to make music unless you understand what a note is. And by the same token, you cannot understand the biological world without understanding what a gene is. A gene is a powerful and dangerous idea. It is a piece of information that moves to the biological world, allowing or enabling biology to function, allowing and enabling organisms to realize what they can and cannot do. It is also a locus of health and disease. It is the way that we are made. It is the information that builds us.

Siddhartha Mukh...: And so, the comparison is that both... In a peculiar way, we're realizing what some scientists from the 1940s and 1950s realized, which is that information is the central currency for the biological world, the central currency for the world of computers, and of course, for the whole universe at large. It's all information.

Robert Pearl: It's 20 years from now, 2040, where is genomics and precision medicine?

Siddhartha Mukh...: Well, genomics and precision medicine have moved along in many ways. Some of them have been powerful, some of them have been disappointing. It's a very broad question. Let me divide the question into two main categories, one of them, which I would call a reading, and one of them which is called writing. By reading, I mean, we have 3 billion odd nucleotides in our genome. Three billion letters is what the human genome is written from, and then only four letters in that alphabet, A, C, T and G. One challenge was to figure out whether we could use those four letters to predict who is going to be well and who's going to be ill. What illnesses will come in our future, and how to link those and predict those as we move further along?

Siddhartha Mukh...: We are learning to do this. For simple diseases, and by simple I mean, diseases that are caused mainly by alterations in a single gene, we have made vast progress. So, think of cystic fibrosis, think of Huntington's disease, and other diseases where we've made vast progress in identifying patients who are likely to develop the disease, or already have the disease currently. But for complex chronic illnesses, such as cardiac illnesses, heart attacks, or even complex chronic conditions such as obesity, diseases such as breast cancer, we're beginning to understand that hundreds, maybe even thousands, of genetic variations in the human genome can predict the future likelihood of you having that disease. And once we learn to predict that, our capacity to deploy precision medicine to those patients will increase enormously. It's already increasing.

Siddhartha Mukh...: So, the hope was that we would learn very quickly the rules, as it were, by which the human genome increases risks for disease. But those rules have turned out to be more complex than we had imagined. So, let me give you some more positive things. Gene therapy is alive again. There were mistakes made, ethical mistakes, medical mistakes made in the 1990s and 2000s, when we tried to use gene therapy in humans, replacing genes, altering genes in cells, such as blood cells, a little too quickly. And that froze the field for about 10 years, 15 years, but it is alive again. And for diseases such as sickle cell anemia, such as hemophilia, these gene therapies have turned out to be transformational. There're early days still, but we're seeing extraordinarily positive results in these areas. We may be able to cure sickle cell anemia and other diseases such as hemophilia and beta thalassemia using gene therapy.

Siddhartha Mukh...: That's a remarkable moment in human history. These diseases that have haunted us for generations, for decades, for millennia, we might be able to cure using gene therapy, and we might be able to cure them safely. There were mistakes that were made, as I said, in the 1990s, that really froze the field. The field is now back up and running again. And the early results have been extraordinarily promising. So, in terms of that, identifying patients who have the diseases, these illnesses and treating them, we are really making rapid and fantastical progress. Finally, let me talk about writing the human genome. This means making deliberate changes in the human genome that allow us to specifically go into that library of 3 billion nucleotides that the human genome possesses and make specific changes in it.

Siddhartha Mukh...: In the last 10-odd years, we've discovered tools such as CRISPR, Cas9 and several others, that allow us to make very specific changes in the human genome. We don't know how safe these are, but for the most part, they've turned out to be quite safe. And for diseases such as, again, sickle cell disease, or beta thalassemia, and some others, there are trials ongoing, which will show us whether this can be used safely or not. But I cannot emphasize enough how revolutionary these technologies are. These technologies allow us to alter the human genome, our own genomes, we have become machines that can alter our own codes of instruction. And that's extraordinarily powerful. And of course, it raises many, many ethical implications, many of which are answered in the film.

- Jeremy Corr: In the coming years, maybe 5, 10, what do you see the biggest ethical debates around genomics going to be?
- Siddhartha Mukh...: Well, the ethical debate that we need to handle is to figure out whether or not to do genetic engineering in human embryos, sperm and eggs, and under what circumstances. We know that the Institute of Medicine and other institutes believe that this should be only done under conditions of extraordinary suffering. But what does that mean, who does that apply to? Is a major question. The second question is, how safe is it? If we do it even in blood cells, cells that don't transmit their information to the next generation, is it safe to do it? And how can we assure ourselves of the safety? The third question is cost. These technologies come with enormous prices when they become drugs, who can afford it? And will we be able to afford these?
- Siddhartha Mukh...: The final question is around precision medicine. Is there a mechanism by which we can make... As we learn more about genomics, can we make our medicine more precise so that we don't give indiscriminate medicine to people who are unlikely to benefit from it, and give it only to patients who are likely to benefit from it? And if we do so, how do we do this in a way that retains or restores the faith in the economics of medicine, which is now in a very bad place?
- Robert Pearl: Your book, "The Emperor of All Maladies," not only was a New York Times bestseller, but a Pulitzer Prize winner, that's been seen as one of the greatest hundred books of nonfiction that have been written. I loved it. A question that I have thought about often since then, was really to understand the pioneers who began the field, and every day inflicted what must have been terrible pain on children as they tried to figure out the right dose of medication that would save their lives rather than taking it away. Can you provide some thoughts about what it was like for these people, and why you believe they were able to accomplish it, when it had never been done before?
- Siddhartha Mukh...: Well, I know many of them, personally, in interviewing them for the film, for the book, and we have become friends, some of them unfortunately, have passed away. There was a can-do spirit in medicine, and a desperation around cancer which still exists, but has to be reignited which these people, all of them remember. Virtually, every one of them remembers a time when they were at the National Cancer Institute, where they really felt as if there was a sense of camaraderie, there was a sense of, let's defeat this thing.
- Siddhartha Mukh...: And so, we need to get that can-do spirit back in medicine, we need to get people enrolled in clinical trials. Medicine has become to some extent... If you look at the esprit de corps, as it were, the spirit in the field, people feel defeated. They feel defeated by the economics of medicine. They feel defeated by the amount of documentation that they have to do, they feel defeated by insurance, they feel defeated by malpractice laws, they feel defeated in every single way. We need to reinvigorate the spirit if we want to make progress.

Siddhartha Mukh...: And I feel very strongly that we need to learn from these pioneers, because these pioneers were the ones that really moved the needle on the early days of cancer medicine. And virtually, all of them say the same thing. They say that, we felt as if we were part of a group effort, of a large effort, and we felt valued, we felt that society valued us. I'm going to say something controversial here, but it feels as if society now values money. It values bankers, it values products, social media. These help in minor ways, I suppose. But the real value that we should be putting--and the pandemic has reminded us of is--is of the people who put their lives in front of themselves and help other people. I'm moved to tears every time I hear of a doctor or a nurse on the front lines without protective equipment, who has been infected and is dying because they put their lives in front of the lives of others.

Siddhartha Mukh...: A society which does that is fundamentally wrong. There's something wrong with us. And there will be an autopsy, there will be a dissection, a biopsy, of what has gone wrong, what went wrong with us as human beings, as a society, once the storm blows over. And I hope that one of the elements of that autopsy reminds us that medicine is an occupation that demands a level of sacrifice. And these men and women perform that sacrifice for you, for us, for our parents, for our children, for our loved ones. They did it during the HIV pandemic, they've done it during this pandemic. We need to restore their spirits, we need to respect them. In Spain, every evening, and I'm tearing up as I say this, at 8:00 p.m. when, in quarantine, they open the windows and they clap for the medical personnel on the front lines. We have devalued medicine, and we are paying the price for it.

Robert Pearl: I couldn't agree more with you about the sacrifice. As you know, from studying history, it goes back to the plague, the times before that, we saw it in the '80s when we didn't understand AIDS. If it makes you feel a little bit better, the people in the house across the street from me, have nothing to do with me, but just their house, have a big sign thanking all the physicians and nurses and respiratory therapists who are dedicating their life every day to caring for their family and friends who are suffering from COVID-19 without the protection they need. Let's go back for a second, if we could, to the cancer experience, I'd love to have your thoughts on how our... on why we've been so successful at improving outcomes in what I'll call the blood cancers, and why we've had so much difficulty making really almost any progress in these solid organ tumors?

Siddhartha Mukh...: Well, if I knew the answer, I would tell you, but unfortunately, I don't know the answer. I think that blood cancers have been very deeply investigated and there's a long history of investigating them. In blood cancers, we can use biopsies to figure out, because blood is a liquid organ, we can just take blood from a patient and use biopsies to figure out how these patients are doing. But you're right, it's somewhat of a mystery why blood cancers have been more amenable to therapy than many of the solid tumors. If I knew the answers, I would tell you. I have many, many, many theories, they would take a whole hour of discussion about how blood cancers differ from solid tumors. Solid tumors seem to recruit around themselves a shell, as it were, of responses or

defenses against the immune system and against drugs. Blood cancers are maybe, less able to do so, that may be one reason. It remains a mystery as to why some of these blood cancers have been more amenable.

Siddhartha Mukh...: Let there be no mistake, there are blood cancers that are lethal, acute myelogenous leukemia, and some of its cousins, aggressive or high-risk myelodysplastic syndrome are lethal diseases still. So, it's not as if every blood cancer is responding, only some are. ALL, the acute lymphoblastic leukemia, the typical cancer, the blood cancer that we see in children, has been one of the cancers that's been very responsive. But there are other cancers that have been not that responsive even within the blood cancer world.

Robert Pearl: You are an amazing researcher and a clinician and yet you find time not just to write, but to research in remarkable detail, areas of tremendous complexity. How do you find the time in the day, week, month and year to accomplish so much?

Siddhartha Mukh...: Well, look, it's not like I'm accomplishing everything. I'm trying to do the best I can. One of the things that I've done is, I've shrunk my laboratory. People like to expand their laboratories, I've shrunk mine to focus on what I consider the essential questions. Unlike most people, I have been lucky to be spared the sort of publication rat race. I try to publish papers that have impact on the field, but I don't try to rush anything. And then, I just carve out specific time for my writing. This work is my life. It is also in its own way... I don't want to be grand about it, but it's in its own way... I've had to sacrifice other things to do it.

Siddhartha Mukh...: My day begins with thinking about my patients and thinking about the trials that I'm running, and thinking about the experiments I'm doing, and thinking about what I'm going to write about next. And there are sacrifices all along the way. I mean, if I had just done only one thing, it would have been an easier life. But I enjoy it. I'm not doing this because someone has forced me to do it, it's just because I enjoy all aspects of it.

Robert Pearl: Sid, any last thoughts for listeners?

Siddhartha Mukh...: I want to refer to Warren Buffett's famous line, "When the tide goes out, we discover who has been swimming naked." American medicine, it has become clear for the last five years, has been swimming naked. And we need to figure out how to stop that nudity. Every system that was supposed to work broke in the early days of the pandemic. We need to figure out, as we recover, how to fix those. And only if we fix those can we become the superpower and the global leader of economy that we once were, and we hope to be again. All I can say is that, this pandemic has been an X-ray or an MRI that we performed on the American medical system. And all the silent aneurysms and the hidden malignancies that were hidden for some people have become apparent. Unless we fix them, we are not going to return back to the same level of normalcy that we had before.

Robert Pearl: Jeremy, Sid is a brilliant thinker, researcher and writer. He and I are in complete agreement about what must happen over the next couple of months. We must avoid the massive tragedy that would ensue should our hospitals become overwhelmed. And as a result, patients die not from the virus itself, but as a result of our inability to provide the intense medical treatment that might have saved their lives. I too feel, it is irresponsible and inappropriate for our nation to ask doctors, nurses, respiratory therapists and others, to render care without the protective equipment required. As someone commented on social media, we never would send a soldier to battle wearing only a bathing suit. There's no reasonable defense that can be made for our nation's delay in preparation, and the shortage of testing kits, N95 masks and ventilators.

Robert Pearl: Sid and I may disagree, however, on one point. He believes that we will have effective medications capable of stopping the virus, not just helping patients in the most critical conditions, but stopping the virus in the near future. I hope he's right. But I feel we're looking at a year, not three to four months, for a vaccine or a treatment that will have the major impact that will be necessary to help people avoid getting the infection in the first place, or to be able to cure it in a very quick time frame. As such, I believe we need to select a decision date sometime by the end of May, let's call it a "D Day" for Decision Day, at which point we will have a specific plan in place to slowly but surely reopen the country, and to begin safely pulling back on social distancing requirements. Of course, if there is a drug that's only a month away, we may delay the plan at that time, based upon the available data. But if not, I simply do not believe that we can go a full year of the social distancing that exists today, and the economic shutdown impacting families and small-business owners.

Robert Pearl: For the most vulnerable people, the elderly and those with multiple chronic diseases, they will need to continue to be self quarantined until a vaccine is available. The risk to them is just too great to move ahead more quickly. However, for those individuals who are healthy, I fear that the damage of prolong social distancing will be worse than the effects of the virus. Of course, we can only reduce the extent of social distancing if we are able to fully stock up and equip our hospitals, to protect the doctors, nurses, and staff caring for the patients with COVID-19. And we must be certain that in each community, we have the necessary resources to meet the medical needs that will result from the increase in cases that will invariably come as we limit social distancing.

Jeremy Corr: As a business owner in Iowa, I concur that the psychological, interpersonal and economic consequences for people and their families are reaching a breaking point. As you said, our nation needs a clear, scientific and broadly understood plan. Anxiety and uncertainty are prescriptions for fear and panic. More on this, on this week's Coronavirus: The Truth podcast.

Robert Pearl: Please subscribe to Fixing Healthcare on Apple Podcasts or other podcast software. If you liked this show, please rate it five stars, leave a review. Visit our website at [fixinghealthcarepodcast.com](http://fixinghealthcarepodcast.com). Follow us on LinkedIn, Facebook and Twitter @fixinghpcpodcast. We hope you enjoyed this podcast and will tell your

friends and colleagues about it. If you want more information on these topics, you can visit my website, [robertpearlmd.com](http://robertpearlmd.com). This is the time for all listeners to take care of themselves, maintain social distancing. If you develop symptoms of a cough, fever, headache, please call or set up a video visit with your physician.

Robert Pearl:

If you develop more severe problems, difficulties breathing and chest pain, contact your physician as quickly as possible. Social distancing creates stress for individuals, for relationships, for communities. This is the time to stay together. Once we have a specific date at which we will be making the right decision based upon scientific objective metrics, with a clearly defined approach that our nation will follow, we can slowly return back towards normal. Working together, we can make American healthcare once again the best in the world.

Jeremy Corr:

Thank you for listening to Fixing Healthcare, with Dr. Robert Pearl and Jeremy Corr. Have a great day.