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**WILLIAM  
BONVILLIAN:**

So I try to do this at least every other class so we remember the context. But class 1, as you remember, was all about the economic growth theory and the economic growth context for innovation policy. And we did growth economics and how it broke away from classical economics around developing a new theory of growth. So Solow argued that there's technological related innovation. And we concluded that was a key direct innovation factor. So we could loosely, although in accurately, translate that concept as saying, you've got to do R&D.

And then we read Romer. And Romer argued that behind that R&D system is human capital engaged in research. That's another foundational direct innovation factor. You can't build an innovation system without these two elements arguably. So it's the R&D and the talent behind it. Those give us two direct factors.

Then in class 2, we talked about the indirect elements in this larger ecosystem. And government controls some. Private sector controls more. But that gives us an idea of looking at innovation as a system, which Richard Nelson contributed to. And then within that system, you look at the strength of the innovation actors. And you can begin to think of your innovation organization as a third direct innovation factor. And that leads us into the whole problem of how do you cross the valley of death if you've got a disconnected model.

Classes 3 and 4 were case studies on manufacturing. So we took a deep dive into a very current set of practical, ongoing problems to try and think about some of those innovation organization lessons in a manufacturing context. Class 5 was explicitly about innovation organization. And we looked at David [? Hart's ?] analysis of the ideology behind looking at innovation in the political system and the conservative, the associationalist, which is the public private, the national security models. All those issues are still very much with us.

And in that class, we also talked about Donald Stokes' work where he critiqued the split in the US innovation organizational system between front-end innovation, the R side and the later stages. So when we organize to do, essentially, a research model at the end of World War II

under that pipeline model that Vannevar Bush gave us, we missed issues that subsequently rose in the economy and became really deep sources of problems about the connections to the fall of one implementation back into the innovation system stages.

Class 6 was about crossing this valley of death. How do you build the bridging models that get you from a pipeline innovation model across to the later stages. That's not easy in our system. And then we also talked about the fact that we run two parallel systems in the US. So Vernon Ruttan's book, *Is War Necessary for Economic Growth*, introduced us into the whole Defense Innovation system, which is not disconnected. That's a pretty connected model.

And the Defense Department will typically perform the research, the development. It will do the demonstration. It will do the test bed. It will move to the advanced prototypes and will often provide an initial market for emerging technologies. That's a very different organizational system as we discussed from what the civilian agencies are up to.

Class 7 was innovation at the face-to-face level. That's our whole great group's theory. So if innovation has to do with institutions, which it certainly does-- how are those institutions organized and how do they connect and how are the handoffs between the actors? But in the end, people own innovation, not institutions. It's very face to face. And then in the great groups classes, you remember well we talked about some of the rule sets that tend to guide the way in which great group-based innovation operates.

And again, that drives us back to this third innovation factor-- what does innovation look like an organizational point of view, from a systems point of view, from an actor's point of view, but also, how does innovation look at the face-to-face level. And then in class 8, we talked about DARPA, which is an institution that actually attempts to do both on a good day.

It will support that connectedness of innovation institutions being connected using that defense model. But it will also attempt to build great groups. And we talked about JCR Licklider and the evolution of the IT revolution, a lot of the origins of which came out of DARPA-supported research as an example of that.

So now, we're going to do some more case studies in today's class really looking at the life science innovation system and how does that function. And we're going to take a lot of the lessons that we've been learning and try and fit them into analyzing this really important piece into this territory.

Let me give you a quick NIH historical backdrop. Remember the pre World War II and the World War II context? NIH just stood up as a Vannevar Bush basic research organization. So Franklin Roosevelt in Vannevar Bush see what happens in World War II. They see the development of antibiotics led by penicillin. And the effects are breathtaking, absolutely breathtaking.

So suddenly, we fight a war. And you probably won't die of disease. You'll actually die of battlefield injuries, which has never happened before. And that immediately has an effect. It removes pneumonia from the number 1 cause of death in the United States conceivably further down the list. It's very dramatic. Bush and Roosevelt see this and understand how powerful that model is.

And so one of the theories in The Endless Frontier that Vannevar Bush puts out, as you remember, is that there's going to be a war against disease. And they've just seen what this model is. So they want to do it. Now, Truman, as you remember, vetoes the one agency, One Tent National Science Foundation role. So he vetoes that in like, is it '47 or '49? And that leaves a void.

So voids tend to get filled. So this little research outfit that's part of the Public Health Service, the National Institutes of Health becomes the National Institutes and really starts scaling up. So follows a Vannevar Bush basic research model. But it evolves in this gap of organizational leadership in a way and fills that void. And then over time, disease groups tend to be very active politically.

If you have a disease or if a loved one has a disease, you tend to be very active in the disease group. And these disease groups push their disease in Congress. And Congress keeps adding institutes and centers onto the model. When it reaches an unmanageable number of 27, finally, Congress actually tries to restrain itself. But it creates an organizational model that's problematic.

Now, another feature here is-- here's a line from Tony Fauci. It's one of the-- He's the director of NIAID, quite famous. NIAID was one of the leaders in getting on all kinds of infectious diseases, including AIDS. But Tony Fauci writes in 2003, "the path to product development has not been a part of NIAID's research strategy." In other words, that's not on the table. They're worried about their basic research results.

So what did NIH-- and arguably, the biotech model that is spawned from it-- what did they get

right? And they get a lot of things right. It's an amazing system. It's a remarkable story of success. So even though we're going to be critical today, it is an amazing success story. NIH trained everybody. It created this huge education system that put a lot of talent on the task in Romer's terms.

This knowledge base helped spawn a remarkable entrepreneurial biotech startup model. And we talked about Genentech during our great groups class. That's the first. But that's a very good example of what then flourished. And Boyer and Swanson were the founders. Boyer comes out of that NIH-funded system.

Biotechs have been able to get venture capital support even though they have a 10 to 15 year stand-up model, which is a remarkable accomplishment. No other sector is able to get venture capital money unless they're no more than a couple of years out of production. Biotechs have been able to break that and get long-term support for R&D.

And the key to this has been the value of IP. So there is a working monopoly model in the biotech sector. So if you're first to patent a new drug, you are given a monopoly rent for a 20-year time period minus the time it gets you to get through clinical trials with NIH, which can be seven years. So it's a 13-year run where you're assured of monopoly rents.

And unlike the hard technology sector, it's harder to stand up, in effect, copy-cat fixes, copy-cat drugs. So you really do get a significant run typically if you're first to patent and you get ahead first through the clinical trial process. So that's been the enabler that allows this financing system to work. The other key feature is FDA's approval.

So FDA gives you-- in stage 1, stage 2, stage 3 clinical trials, if you're developing a cancer drug, you know exactly what your chances are on getting through the from stage 1 to stage 2 and stage 2 to stage 3 and from stage 3 to final drug approval. You know just what your chances are. So that enables venture capitalists to tee off their stages of financing to your success in the clinical trials process. There is no benchmarking system like this in any other sector in the economy. It works amazingly well.

And then another big difference between life science and everything else is that, if FDA approves your drug, you are guaranteed a market. In fact, our wonderful legal system is such that, if a doctor fails to prescribe the medicine which is fitted to your problem, the next day, the doctor gets sued. So there's this huge forcing mechanism in the system. There's nothing like a certification that guarantees you a market on the next day. There's nothing like this anywhere

else in our system. It's a remarkable thing.

And we can start to think about how do you get analogous certification processes and benchmarking processes in place in more physical science-based technologies. It would be very interesting. We haven't done it. But there's a lot to be learned from this sector because of the system it's setup.

Upstairs-downstairs has historically been a problem, particularly in European science, but also in US science, whereas the academic researchers have disdain for the company researchers. That has really broken up and broken apart in the life science side. So outstanding academics, think Boyer, who spent time in a biotech.

That's not created as a sound career path. Boyer had to break the ground. He got a lot of flak for it at the time. But over time, it's become accepted that you can have an academic career, move to a biotech, move back to an academic career. That's OK. Obviously, this conflict is used throughout that whole process that had to be dealt with. But that's an acceptable pathway.

So the whole upstairs-downstairs relationship between the academy and commercial development has really been broken up. So that's another thing that this sector got right. NIH also has a huge amount of money. It's by far the largest R&D agency. It's got over \$30 billion a year. Nobody is close.

NSF, by comparison, has \$7 billion a year. The Department of Energy Office of Science has \$5 billion. DARPA has \$3 billion. So this is an order of magnitude almost different from other R&D agencies. So the political constituencies, including the disease groups, have built a very powerful political base for sustained funding in this sector.

Now, that's the good news. Here's the problem. We're going to talk about the innovation train wreck that lies ahead here. So the economic model for biotechs and pharmas really requires blockbuster markets. It's a huge problem. So in other words, third-world diseases, infectious diseases, small-population diseases, it doesn't make sense to pursue those.

To get a drug through the FDA clinical process to develop in time before, during, and during the clinical trial approval process itself, that's around a \$1.4-billion-or-more proposition. So unless you're selling it to a major market, it doesn't make any sense to develop the remedy.

So there is a statistic that some cite, which is that 80% of our R&D money in life science is spent on 10% of the diseases. That's a problem. I don't think the number is that bad. I think that's exaggerated. But we've got a problem here because of this blockbuster drug model. Only if you're developing a drug that sells into a major market opportunity is it going to get into the market.

So what does that leave behind? In addition to the things I've mentioned, the precision medicine or personalized drug model gets left behind. In other words, if each one of you is going to have their own remedy variant that's particularly adapted to your genetic structure or metabolism or whatever, what are we going to do? Run a \$1.4-billion clinical trial process for you? It's not going to work.

So how do we deal with this? There's a huge looming train wreck problem in the system because that's where it's going. These are the benefits of being able to use big data and analytics to develop personalized medicine. But if there's not an economic model to get it there, it won't happen.

The litigation threat makes drug companies risk averse. So we leave a lot of promising stuff on the table because of that threat. Often, a drug will cure, let's say, 20%, 30%, maybe 40% of a disease group's problem. But if it kills some people, we'll never go to market because we don't understand the precision medicine, the personalized medicine implications of these things. And until we do, we're just leaving a lot of stuff on the shelf that has potential value because Americans, for good reason, have very low tolerance for risk from drugs.

The health care spending in the overall system by 2025 may account for 9% of GDP or more. And we'll talk about this in a minute. But we can't afford a health care bill of those dimensions and still have other things going on in the society and the economy and the government.

This is what we spend money on in the federal government. This is what we think of as government. So that's like the national parks and federal research, transportation, highways. That's this. That's defense. So that's actually about 16%. And that's now about maybe a little below 20%.

That's Social Security. That's Medicaid, Medicare, and SCHIP, the big health-care-oriented entitlement programs. That's other safety net programs, 9%. And then we have interest on the debt, which is actually now over 9%. So as you can see, the federal government is mostly-- we're talking 60% plus interest in the debt-- a check-writing kind of organization. And that's

what we think of as government. And that's what we think of as the domestic side of government. So these are pretty small pieces. Rasheed?

**AUDIENCE:** What year is this for?

**WILLIAM BONVILLIAN:** This is probably about four years old now. But the numbers are slightly even more problematic than these. So again, this category is now 16%. So the numbers are probably off by a couple of percent. But it's a problem. And as we'll see in a second, these are components of federal spending. So that's health. And that blue line is everything else. So you can see where taxpayer dollars are going.

This kind of demonstrates that Social Security is not the real problem. It's really the health care cost related to Medicare and Medicaid that are the problem. This shows historic levels of taxation. Remember, the United States was founded on a tax revolt. So we're not going to have European-style levels of taxation in the United States. It's just not going to happen. And we start to run into real political trouble once you get a little bit above, say, the 20% level of taxation that's a percentage of GDP.

So we're headed way up against that threshold largely because of the demographics and the health care spending, which means that, broken down this way, the percentage of GDP we spend on, what we consider most of government, is just not going to be affordable given the acceptable levels, around 19%, 18%, the acceptable tax range in our political system. So Max?

**AUDIENCE:** What are [INAUDIBLE]?

**WILLIAM BONVILLIAN:** Expenditures by the federal government. What they're spending in a given year. What they were actually outlaying to meet their costs, to meet their obligations. So these are some of the problems that lie ahead. We got a real fiscal train wreck because of the cost of this health care system driven by the demographics.

My generation attempted to make you spend all of your money on me. That's essentially what's going on. It's a massive intergenerational transfer of wealth. And you guys need to wake up to that because it forgoes opportunities that you have. And at the heart of this is a really serious problem with health care expenditures.

So let's now get back into our main themes. This was a classic 2003 report, what is now called

the Academy of Medicine. It used to be called the National Institute of Medicine. It's part of the national academies-- they did on evaluating NIH. And it was a pretty startling criticism. And they looked hard at this NIH system. It really began to identify some of the problems.

Interestingly, this report drove some interesting congressional reform attempts. Let me see if I can summarize a few key points here. And Chloe, did you have this one? You've got it, Martin? OK. All right. So as I said, NIH is more like a feudal barony. It always has a famous director. But they don't have that much control over these institutes and centers. There is no centralized budgeting. And the institutes and centers battled to protect their percentage share of NIH's total budget.

So Harold Varmus, a famous former director of NIH, who later came back in the Obama administration as head of the National Cancer Institute, he said, in 2001, "NIH would be more efficient and more manageable if a far smaller number of larger institutes existed organized around broad science areas." Less institutes, organized around science areas is his twin points here. And there's a lot to be said for that case. Instead, as we discussed, the institutes got set up essentially at the behest of disease groups to solve their disease problem.

It turns out there isn't a separate pathway for each disease. It turns out there's a lot of common pathways across a lot of diseases. And we don't have a very good mechanism in NIH for getting groups of institutes to collaborate on a cross-cutting set of problems. So fundamental organizational issue.

Now, there is another side of this argument, which is, you've got a lot of institutes with a lot of freedom to do a lot of stuff. Maybe a desegregated model is not all bad. There's certainly a case to be made for that. But overall, there's a challenge here. And NIH's budget doubled from 1998 to 2003. So there was a federal surplus in its budget during the IT revolution, which was generating huge amounts of tax revenue.

And two US senators saw this emerging surplus. They were on the appropriations subcommittee that handled NIH. And they went to the Senate floor and took a noticeable part of that surplus and gave it to NIH. It was a fascinating political development, very shrewd. Arlen Specter of Pennsylvania and Tom Harkin of Iowa were chairmen and ranking on the appropriations subcommittee. And they created the doubling. It's a remarkable story.

They were able to do it because there was so much excitement at that time over the genomics revolution. So we talked about Venter and the NIH dueling battle [? Collins ?] over who's going



to get to the genome first. There was creating huge excitement. It was a sense that this medical research could lead to all kinds of new fundamental understandings. Everybody was excited about the idea. And that enabled those two senators to double NIH. No other agency has ever been able to do anything like this. The rest were stagnating.

But the demographics are changing. The patterns of illness are changing. We have a threat of biothreats. Is NIH too fragmented to cope with all these challenges? Can it respond quickly enough? These are all issues that the report raises. It wants to avoid proliferation of new agencies. And in fact, Congress did that as part of its reform legislation. You can't have a new institute in NIH unless you close down another one.

The Institute of Medicine, and now the Academy of Medicine, urged in this report that NIH focus on its capabilities. And it needed to do so because it concluded that NIH is not only imperfect, but nobody would have ever designed NIH this way at the outset. And in fact, Elias Zerhouni once told me in a meeting and others, if only we had thought through the organizational model before we doubled. So we doubled first. And then there was a mad scramble to grab the money from the existing institutes. If only they had thought about the organizational model up front.

Zerhouni led a great effort to try and get cross-cutting research efforts going across the institute. So he created what he called the roadmap. But essentially, then Congress later institutionalized that as the common fund. Take a little bit of money from each institute. Create a common fund in the control of the director who can then allocate it to the highest cross-cutting priorities. So that was a significant reform. But it's still a very modest amount of money.

NIH needs to pursue an ability to go after high-risk, high-return projects. That reaches a certain stage. And we'll talk about this more later. But peer review is not good at taking risk. If there's a certain level of competition, if the award rate gets higher than about one out of three, your ability to identify breakthrough opportunities that are feasible gets harder.

So it tends to default to-- when there's a lot of competition for an award, the one that the peer community is most confident will yield results, albeit they be incremental results. Why take risks on high flyers when you've got to get the basics done. And so many people are fighting for the money. So this is a huge problem at NIH. How does it take the necessary risks that need to be taken in innovation?

So since then, NIH has been working on creating categories of higher-risk projects that have a

separate kind of review process than normal projects. So there are positive NIH capabilities. We talked about how decentralized can be an advantage. We talked about many setting R&D priorities. You get a lot of safety nets here. There are benefits to investigator initiative grants. You don't want to just have large-scale projects. You want bottom-up opportunities. The issue for NIH, though, is, historically, it's been totally dominated by bottom up and has a modest number of cross-cutting projects.

Peer review in some ways is like Winston Churchill's definition of democracy, the worst possible system except for all the others. So peer review remains competitive. And that's a very important feature to build in. So [? IOM ?] recommended much more centralized management giving more authority to the director of NIH, getting the director to engage in strategic planning across the institutes so they got on to cross-cutting plans, doing cross-cutting budgets. So this idea of take 10% of the budget and fund the strategic plans, actually, Congress worked on implementing that through the common fund.

Strengthening the control of the director over these cross-agency initiatives was key. They also recommended creating a DARPA within NIH to go after the high-risk, high-reward projects. They wanted improvements in NIH as intramural programs.

So NIH is also a major research entity itself. It's not just funding universities that historically has tended to be somewhat weaker than the university research, which is much more competition-based rather than kind of entitlement-funding-based. They wanted to strengthen that. There is a desperate need for standardization of data and information systems across these different institutes. Because a lot of these diseases are related, they can learn from each other and you can't do cross-cutting data analytics.

So there is a series of reform steps here. As going back to some earlier points we've made in the class, NIH is not a connected organization. It's an early-stage basic research organization. It's not connected to the following stages. Now, it has managed to create a model through biotech companies that are venture funded that is able to get across the valley of death if you've got a blockbuster drug. That's pretty creative. Other agencies haven't come up with that.

It's not as if NIH was sitting around figuring it out. But in effect, it occurred and the training of the talent helped it occur through people like Boyer and Swanson. Martine?

**AUDIENCE:** Will we define blockbuster drugs as the one that makes a lot of money or one that impacts the

disease that a lot of people have?

**WILLIAM**

**BONVILLIAN:**

One that makes a lot of money. Right. I mean, in theory, it won't get through FDA unless it actually solves a problem. NIH is primarily small-grant research and lacks the capability to set up initiatives across the stovepipes as we've talked about before. It tends to be fairly slow moving.

There's a risk in peer review of avoiding high-risk, high-payoff approaches. There's limited connections to industry. In other words, that translational research effect is hard to do it at NIH, although Collins, who's the current director of NIH, has worked on creating a special translational medicine institute designed at that problem. So NIH has been taking steps on this.

I think that's a pretty good-- I'll give you one more example-- nanotechnology. The earliest beneficiary of nanotechnology was probably the semiconductor sector. But the life science sector, the health research sector was very close. Huge potential, opportunity spaces in understanding things at the nanoscale here.

Because of the disaggregated structure of NIH, for many, many years after the nanotechnology initiative was created, NIH-- by far, the largest research organization-- was only spending a fraction of what the National Science Foundation was spending on nanotechnology, even though the gains for the health research system were, and clearly are, phenomenal. So that's an example of a problem in being able to attack a whole new approached disease across this very disaggregated model.

So that's the IOM report of 2003. We've learned some lessons from this. We tried to make some changes. And Congress has actually provided a fair amount of leadership on that in creating the common fund and capping the number of institutes. Martin, you want to take us through some questions in this?

**AUDIENCE:**

Do you actually want to do the Cooke-Deegan one? Because that way I can just integrate them. And it might be easier.

**WILLIAM**

**BONVILLIAN:**

All right. We can do Deegan and do it together. And we don't need to spend a lot of time on this because last week's class was on DARPA. So I'm not going to recap this. Robert Cooke-Deegan was deputy when Watson was heading the Genome Project at NIH. So he knows NIH from the inside. He later went on to head Duke's Genome Institute. So he's an outstanding

researcher.

And now, he is teaching science and technology policy at the Washington branch of Arizona State. So he's gone over to the dark side of science policy where people like me inhabit the world. But he's got real talents, unlike me actually, on the technology side.

And he wrote this piece back in 1996 fairly fresh off his own NIH experience, Does NIH Need a DARPA? And I can't tell you how controversial this was. NIH has always viewed itself as better than everybody else. And the fact that one of their own, the deputy director of their Genome Project, was telling them there was a better model out there that they ought to at least consider adopting for part of their operation-- certainly, not for all-- was a powerful message.

And we know the DARPA story. So I'm not going to recap that. Robert Cooke-Deegan underscores that the DARPA model suggests that peer review is not the only way of organizing research. DARPA has far lower transaction costs than NIH does, a lot lower review costs per science direction.

He introduces this issue of how conservative peer review gets when it gets to an award rate that's much worse than about one out of three applications per grants awarded. NIH has got a very limited ability to do the grand challenge model, to pursue that challenge model. It's got limited ability to take high risks and get high rewards. It's got a lower risk acceptance capability. Those are DARPA things that NIH should have-- not all of NIH, but certainly some part of it-- might adopt, he argues.

He cites a lot of examples. The Human Genome Initiative actually originated in the Department of Energy because the Department of Energy understood supercomputers. So for the first five years of the Genome Project, it was carried by the supercomputer gurus at DOE, because they understood what the potential supercomputing was going to be in figuring out the genetic structure.

NIH only picked it up when it saw the promise of the model. NIH had terrible trouble coping with the advances made by Leroy Hood. And we'll talk later about Venter and how do you adapt and incorporate a computational model in medical research. They're locked into a biology-only drug development model pretty much. It's hard for them to do other territories as we'll talk about when we get to the convergence report.

So the lessons from DARPA for handling multidisciplinary approaches in bringing in a group of

talent around a problem that comes from different fields, there's lessons here for NIH. I mean, that's the heart of Robert Cooke-Deegan's recommendations. And Martine, it's yours.

**AUDIENCE:** So I think you did a good analysis of the papers. So I won't really summarize too much more. I think we can just go straight into discussion. And so I think a good first question would be, how do we-- know that there's a lot of cost in the health care industry and this system, the structure they have isn't perfect. And so how do we create a system so that these problems that need to get solved but don't have economic incentive because they're not blockbusters, how do you combine NIH with maybe some DARPA-like abilities and industry? And if anybody's specialty is higher research, it would be interesting to get your insight first.

**AUDIENCE:** What you mean by higher research?

**AUDIENCE:** Well, if you're focusing on an academic career in a national lab, you know more about that than I would.

**AUDIENCE:** Where is Lilly when you need her?

**AUDIENCE:** Yes, you got it.

**AUDIENCE:** Yeah, I think you probably, as Cooke-Deegan laid it out, you just really struggle in this peer review process if you have an idea for maybe not a blockbuster drug but a new approach to a system that hasn't really been tried out yet. So that's what you see. [INAUDIBLE] a mentor have this huge problem. And I think it really is just kind of allocating a part of that NIH budget that they get to this DARPA-like high-impact, maybe high-risk research and then moving from there.

But I'm not sure because it takes so long to develop these things, so a three to five year. And then you have to figure out clinical trials and things like that like. Would the time scale need to be adjusted to account for doing the research and then moving into clinical trials to be able to actually support these high-risk initiatives. And a lot of these I feel like will be building on research that doesn't really exist or isn't really there yet. So we'll need more time to stand up [INAUDIBLE].

**AUDIENCE:** Yeah, I think there's probably two main ways that maybe some of the later readings touch on more. But definitely, incentives on the FDA is hard to extend and make that process a little bit more profitable than, say, if it's on an orphan drug where you have a very small market that could be addressed when the drug comes out by increasing the patent life so they have

extended patent provisions for those kind of drugs. That definitely helps make it more profitable.

And also, a lot of the later papers talk about this. But they have a lot of flexibility in the way they can price their drugs. So I think that kind of helps a lot because if they can charge a lot of money for a niche drug that kind of compensates for the fact that you're not giving it to as many people.

**AUDIENCE:** And I guess my concern with that last one is what about a Martin Shkreli situation?

**AUDIENCE:** I mean, yeah. Obviously, that's going to come up because all these companies will want to recoup their costs because they're spending millions and billions of dollars on these drugs to develop them. And there is kind of an argument for both ways that it's kind of justified but, I mean, obviously, bad for society.

**AUDIENCE:** And also, you could make a very similar argument for any other drug in one of these blockbuster drugs as we say. Because well, you can still charge an exorbitant price for them. You can get tons of money for them. And then you're back to square 1 where, OK, let's just keep funding the drugs that we've been doing because don't fix what isn't broken, right? So I'm not sure how it would incentivize people to focus on these smaller drugs.

Now, one way you could do it, maybe tax incentives or something. Maybe force insurance companies to foot the bill a bit more. But I don't really know the detail on how that would work.

**WILLIAM BONVILLIAN:** This is one of the great societal dilemmas that we've get in health care at the moment. You want to create enormous incentives for researchers and the biotech companies they may create to go after these big problems. You really want to incentivize that process. So if you start to disincentivize it, you're going to have less remedies on the table.

On the other hand, you've got serious cost problems for some portion of the population that's not going to be able to cope with the cost structure. And you're going to have real reluctance on the part of government agencies to subscribe for a huge cost burden that only helps a relatively small number of people. So this is a dilemma that is now upon us big time that we have not sorted through in an intelligent way.

And there's constant reviling of drug and biotech companies. But on the other hand, they're the ones that created these opportunities for us. So it's a very contradictory-- the politics

doesn't seem to recognize the importance of the innovation system. And yet we don't have the right balance between the two.

**AUDIENCE:** Yeah, [? I was just going to answer ?] [INAUDIBLE] the policy side, or whatever [? you want to say. ?]

**AUDIENCE:** Oh, I actually was going to say that also I think the dimension that's also missing is something we touched on last week, which is the ethical components. I think there's really a rising bioethics community surrounding issues of utilitarianism versus issues of human suffering. Do we seek to address the person who is suffering the most or the number of people who are suffering? And that is a really difficult, I think, ethical question that has yet to be addressed on a national level.

And I think it's easier-- I guess, I think about it in terms of heuristics, like short cuts for decision making. If we understand what our values are nationally, we can understand where to begin to allocate money. And if we sort out our national values in terms of the life sciences and what we think are our national priorities, perhaps maybe through a referendum-like system, I think it would actually be a much more efficient and accountable way for the government to make funding priority decisions rather than for life sciences organizations and the NIH to sort of make those decisions for themselves or for the citizens.

Because ultimately, this is an issue at the human level. And that implies an understanding of bioethical considerations.

**WILLIAM BONVILLIAN:** I think that tends to run into a problem, however, with root attitudes of the American population. And I would say that a lot of the American population believes that we should be allowed to live forever because we're Americans. So we should be eternal. I'm exaggerating a bit here. But there's a lot of thinking along those lines and a lot of assumptions that any cost, whatever it is, is justified in terms of the outcome for my health.

So these are these are really tough decisions. And the life science system is now right up against this. And the whole innovation model is right up against these. So these are these are important considerations.

**AUDIENCE:** Yeah. Just my concern with the proposal as far as putting it in the hands of American people is kind of what questions are appropriate for letting people to be answering versus the ones that are experts. [INAUDIBLE] A lot of people would debate that the Brexit question wasn't really

something that the average person could understand well enough to make an informed decision.

And so I guess if you're asking strictly what are your ethical beliefs, vote on that. I guess that's something that people can vote on. But if you're given options of should we fund something that will save x number of people at this cost, weighing that information is more difficult than I think the average person is willing to put the time in to understand. So I think that, to some extent, NIH and these kind of organizations need to make the decisions on what our national priorities are but, ideally, with some input from us.

**WILLIAM**

**BONVILLIAN:**

I want to push you back to the issue that's before us in this class, which is the innovation organization model that we've got here. So we're looking at an innovation organization that evolved in a very historical set of ways where the problems, when it was in the foundation level, the scientific problems turned out to be different than the way we see them now.

We tend to see that there are a lot of cross-cutting scientific approaches that cut across many disease pathways that may be critical for those diseases. Whereas back then, we saw, oh, there will be one remedy for each disease, a much earlier-stage scientific notion of disease. And we're caught up in that model. And how do we bring change here? We're up against a legacy-sector problem as we'll talk in a little bit. How do we bring change to that legacy sector from an organizational point of view?

**AUDIENCE:**

I have not an answer, but a non-answer. I am going back to the attack on peer review as it were. I think that's a very odd place to start in terms of something to get rid of. I think there were definitely a lot of reasonable arguments presented in favor of adopting something a DARPA model.

And then going back to your ethics-- you raised the point of bioethics considerations. It seems to me that peer review in the system, appearing to be the values of peer review, are so deeply ingrained in the biopharmaceutical-- well, more on the biological and medical research community. It seems like it's very much part of their values. And it would be very odd to me to see them as separated out because I can recognize all of the detriments of the peer review system and how it can favor incremental, unimportant research over big innovations and risk takers.

But it still seems like, if you remove that barrier, then you might have a flood of ethical problems that would just start cropping up.



**WILLIAM**

Look, I mean, the DARPA model does not work in all circumstances. In other words, the

**BONVILLIAN:**

DARPA model is very much a top-down model. A bunch of elite program managers are looking at things they want out of the end of the innovation pipeline and designing projects to get there. And we can certainly see why there's room for this model, for that kind of projects-based, challenge-based model.

NIH offers the other side of the coin. Researchers propose funding, and they get funded based upon the interest and quality of what they're proposing. That's very much a bottom-up model. In other words, a lot of people can see a lot of stuff in the bottom level that a top-down model can't necessarily see.

So Chloe, you're right. It's not that you want to replace NIH with DARPA. I think what Robert Cooke-Deegan would say is maybe there's room within a large NIH entity for a DARPA like piece. Just as there is in the Defense Innovation System, DARPA is only one element of a much larger defense research portfolio. But it does provide some interesting capability.

And peer review does have advantages from that bottom-up perspective that a top-down strong program manager perspective will not necessarily be able to capture.

**AUDIENCE:**

So from a business perspective, the thing I'm wondering about is-- because there is this trend right now called social bonds, which what they do is they look at the parts of society that are really wasting a lot of money and then they create businesses to solve them. And then they give a return.

That's why I asked about the blockbuster drug. Because you get to find a blockbuster drug is also a drug that reduces a ton of costs for the government. And the business model is the government is saying, oh, we're spending \$100 million here to solve this problem. We're going to send some of that portion of the money to you. And that's a good way to cut the fat.

Because if the major problem is we're going to use all our budget to solve these diseases-- there's probably a disease that's 80% or a huge proportion because it's not going to be a linear relationship with the cost.

My other concern too was when you said that they doubled the budget, this happens a lot in software. So it's hard and unintuitive to understand. But it's like, say we're going to have the lunch. And I say, our budget is \$100,000. Then I have to justify--

**WILLIAM** That would be quite a lunch.

**BONVILLIAN:**

**AUDIENCE:** Yeah, that's the thing because we're not just eating, right? It's like, OK, now, we have to justify the \$100,000. Or a cool example is right now there is a startup in Silicon Valley that spent like \$120 million to develop a juicer. And so that you could only juice with the machine. And then a reporter was like, I call your bluff. And they squeezed it with their hands. And they did it.

So my concern is when you have too much money, you tend to have to justify things. And you come up with this weird logic tree. And you don't really fundamentally solve the problem. In code, if there's a piece of code that one coder could do and you put five people, it actually complicates it. It makes it way harder. And now, you got people infighting. So that was my big concern with that too.

**AUDIENCE:** I think-- and Martin may be trying to get at it. This kind of group theory doesn't really exist or kind of breaks down in NIH because it's really hard to get these cross-cutting technologies and encourage that collaboration. And I think what I really want to see out of the DARPA that they pull is not so much get rid of the peer review but start-- because DARPA has the ability to pull these great groups together and just call on a lot of different folks from a lot of different areas and then direct them towards a specific research problem.

And I think where NIH struggles is, yeah, they might have a call to say we want to get rid of cancer or heart disease. But there are a lot of different folks working on it. And not a lot of them, I would say, probably work together in tandem to really figure out and solve maybe one aspect of that problem for maybe 10 years. And then they focus on a different aspect of how a disease would work in a different lab.

And I think NIH really struggles in pulling together these cross-cutting technologies because there's no one pulling them together. And they just leave it up to the discretion of the researchers and scientists and pharmaceutical companies to come up with incremental advances rather than not only calling for big calls or big research projects but also funding and making it possible for great groups to work on these research projects.

**AUDIENCE:** Max

**WILLIAM** Martin, you want to give us some closing thoughts on these two pieces? Oh, I'm sorry, Max.

**BONVILLIAN:** Did you--

**AUDIENCE:** I actually had a quick question. So given that this was published 21 years ago, give or take, I'm curious--

**WILLIAM** Robert Cooke-Deegan's piece, you mean.

**BONVILLIAN:**

**AUDIENCE:** Yeah. Did NIH ever attempt anything like this? Because we've had some significant time period. Did they at least look at it? Or did they decide, no?

**AUDIENCE:** And also, how much criticism did he get for publishing that?

**WILLIAM** It was a threatening piece to the NIH and life science community, frankly, arguing that there may be an additional model that you all need to consider. So it was not received with open arms. Now, in fact, the current NIH director, Collins, has, early on in his tenure as director, latched onto the problem that NIH has got in doing translational work-- in other words, moving a technology from the basic stage into follow-on sectors and doing the handoff to the private sector.

So Collins began to focus on that problem. And there was discussion, at that time, of doing something like a DARPA. So his effort to create NCATS to do translational medicine, the director that he hired to head that new institute-- and he had to close another one to do it-- actually really began thinking seriously about should there be DARPA-like elements in this new NCATS entity.

Chris Austin who is that director, very talented and very interesting person, however, just didn't have the resource to set up a whole new entity within his NCATS piece. But so it's an idea that continues to kick around here and there. And frankly, I would view it as an interesting additional feature for NIH to do some things that it can't really do without this kind of organizational model. So I think there's organizational lessons here that we can take from the issues we've been reviewing and apply it to a long established research entity to create new things in the model. How about some closing thoughts, Martine?

**AUDIENCE:** I mean, the closing thoughts is that we discussed the NIH model and how it does work for what they're doing but also how there are a lot of blind spots and areas that aren't being touched into I've been trying to solve. And then we discussed DARPA, which might be a good way of solving it. But it seems like it won't fit in well with NIH. But there is a structural dissonance, I would say, in terms of that this form factor does not work for these kinds of problems. And it

might also be the groupthink in the area that affects their ability to solve these kinds of problems.

So it might be better for there to be a DARPA NIH but not at NIH or nearby because it might be too difficult. And also, how do you create natural incentives for the researchers. Because it seems like they do these kind of leapfrogging research initiatives because it's a lot simpler and they have a lot to lose if they do fail. And so how do you create this kind of comfort zone for researchers so that, even if they do fail, to get some kind of reward? And how do they get recognition for that sacrifice of their what you call "academic career."

**WILLIAM**

Right. I mean, that's another issue too, which is having multiple PIs on the problem. It's

**BONVILLIAN:**

complicated in an RO1 award process that focuses on the single PI. Let me go onto the next couple of readings. And we'll do them as a pair. So the Infectious Disease Society of America has this report called Bad Bugs, No Drugs, which essentially summarizes the whole problem.

And then the Food and Drug Administration has a paper on innovation or stagnation, which focuses on some of the problems they face. So let's do those. And Chloe, do you have those? Or Martin, do to have one of those?

**AUDIENCE:**

Do you have-- I know I have--

**AUDIENCE:**

Which one?

**WILLIAM**

Bad Bugs, No Drugs, the Infectious Disease Society?

**BONVILLIAN:**

**AUDIENCE:**

I can do this one. I'm prepared for it, yeah.

**WILLIAM**

All right. Well, Chloe, which one do you have? You have the FDA one? Innovation, stagnation.

**BONVILLIAN:**

All right, fine. OK. I mean, the title gives this story away. And this is the Infectious Disease Society. And they note that resistance to bacteria, I think, as everybody in this classroom knows is very much on the rise.

And again, this report was written a few years ago. Two million people in US hospitals are going to get bacterial infections in the hospital. And 90,000 of them are going to die. That is a staggering number, right? We lose 30,000 people a year in automobile accidents. We're losing three times that many in hospitals. So talk about tolerance for risk. Americans haven't fully woken up to this. So hospitals are increasingly a dangerous place to be.

And only two classes of antibiotics have been developed at the time this was written in the previous 30 years. And one of those is already facing resistance in this kind of endless cycle of build up of resistance that bacterial sources go through. And by the late 1960s, 80% of staff bacteria were penicillin resistant.

And in pneumonia, 40% of the infections were resistant to one drug and 15% to the next three. So this is a serious growing problem. Yet because of the blockbuster drug model, there's no incentive for drug companies or biotechs to go after these antibiotics because they cure the problem. So you take the antibiotic for two weeks, and the problem is solved.

What you want, under the blockbuster drug model, is something that I'm going to have to take for the rest of my life for \$100,000 a year, right? You don't really want to cure it. You want to create incremental advances that manage the problem. Whereas the antibiotic actually cures the problem.

So there's very little incentive since there's no economic return model that works. There's very little incentive to go after these antibiotic problems. They work too well too fast. So it's a very weak return on investment. And successful antibiotics are just too successful to justify the investment cost.

So everybody is aware of this. Elias Zerhouni, who preceded Francis Collins as head of NIH, had this roadmap model. And this was certainly on that list of cross-cutting issues that need to be dealt with. But how do you get around the kind of model here, the economic, problematic blockbuster drug model here?

So I mean there've been a variety of ideas advanced. There was bioshield legislation to deal with biothreats. But it could also bear on infectious diseases. The idea there was, for a biothreat, why would anybody develop a biothreat remedy?

Because the drug would only be sold if there was a completely unpredictable terrible national disaster. So are you going to take all the risks and go through the \$1.4-billion clinical trial process to develop a remedy for something that may well never be used? A similar kind of problem for antibiotic drugs.

So the Infectious Disease Society said, wait a minute. The same model that would deal with biothreats, which is that the government would agree to buy a certain number of dosages, a certain volume of the remedy, at a set price if you developed the remedy. So the risk on the

part of the government is actually pretty low. It only has to buy something if you solve the problem.

But then of course, that's what biotechs do anyway. That's the economic model they work off of. So could the government intervene in this sector and, in effect, really change around the risk-reward model. So ideas like this come to bear here. We certainly haven't solved this problem and remains very much with us but illustrates what the issues are.

This other report from the FDA, Innovation/Stagnation-- Challenge and Opportunity on the Critical Path to New Medical Products. And both these reports, by the way, have been updated. I put the originals in, which are fairly hard-hitting. But they've been updated since then by these organizations so you can get later versions.

FDA does not have its own substantial research arm. NIH does the medical research. Yet we're not doing research on how to get a better, more reliable, and certainly speedier evaluation and approval process for FDA. We don't have that. There's nobody on that problem. NIH does not view that is their problem. They view their problem as developing new drugs, new therapies, not figuring out a safety approval set of problems.

So nobody's really on that problem except for FDA's own fairly modest research budget. So the picture that this report portrays is ongoing breakthrough scientific discoveries that get nailed because the drug approval process isn't receiving new science and new technology advances that would enable it to keep up with these breakthroughs. And we mentioned this earlier.

But the most serious one that's ahead is in precision medicine and personalized medicine where it's developing a therapy or a remedy that's uniquely appropriate for you as opposed to me, a personalized medicine approach. How are we going to do the approval process for that? How is FDA is going to manage that?

So it is a dilemma here in the system. And again, it's an innovation organization problem. We've got an innovation organization that's focused on one set of the problems. And they've got the resources do the R&D on it. And yet we've got a parallel big problem that's jeopardizing the other system. And we don't have the organizational capability of acting on it.

So then this is yet another innovation organizational problem that, when you think about these things as systems, you begin to identify what the gaps are. And here is one. That's probably

enough on this topic. So why don't we go right into some Q&A on this. Martine, you want to lead us on Bad Bugs, No Drugs?

**AUDIENCE:** Yeah. So I guess the main theme of this is their way of using policy or subsidies to incentivize the private sector to take on this problem. Or even is the private sector even the right entity to handle this problem?

**AUDIENCE:** I feel like a little suggestion of having government guarantee to pay for a certain amount of dosages seems like a pretty good fix for it. If you leave the free market alone, these companies, they currently don't have an incentive. So I don't think that's really an option.

**AUDIENCE:** A professor of mine, an economics professor at Wellesley and Cornell is very supportive of patent extensions, which is something that was cited in the report. And she felt like, at least in my understanding, that would very much motivate bio and pharma companies to do research primarily because they're concerned that their patents are going to run out in the lifecycle of the innovation process.

**WILLIAM** And explain how that would work, Steph?

**BONVILLIAN:**

**AUDIENCE:** Oh, man, I don't know that I could do it justice.

**WILLIAM** Just briefly. Give us a snapshot. Or Chris.

**BONVILLIAN:**

**AUDIENCE:** So I think, my understanding of the patent-extension process is that, especially for orphan drugs where it's like under like 10,000 people or something like that-- so a smaller market size or it's targeting children like adolescents, you get patent extensions. And that could be three to five years extra, which is pretty significant in terms of drug companies. And yeah, I think those are the main ones. And there's also breakthrough therapy designations.

And those not only help speed up the approval process, which is really valuable for these companies that really want to push through these drugs really quickly and get it to market. And then they also extend a little bit in certain cases. So there's a lot of different small ways FDA is trying to get more incentive, which is nice to see. I think it's a good policy.

**AUDIENCE:** And to add a lower-order analysis from microeconomics, I think the way that she explained it was essentially-- and all of you may know this. I did not know this until two years ago. So

maybe this is new to someone-- is that researchers, I mean, from the time that they apply for a patent, they have, what is it, 15, 17 years or something like that to commercialization where their patent is protected.

**AUDIENCE:** I thought it was 20.

**AUDIENCE:** 20?

**AUDIENCE:** It changed.

**WILLIAM** Yeah, it did. [INAUDIBLE] is now 20 from 17.

**BONVILLIAN:**

**AUDIENCE:** So it used to be 17. And now, it is 20. And so the way that she explained it to us is that, because a lot of the research-and-development process could take 20 years by the time they get a drug to market, they may have already lost the patent. So it no longer becomes economically advantageous for the company to pursue commercialization of a particular therapy, and thus what Chris was saying. So that's just sort of the small connections.

**AUDIENCE:** Separate concerns sort of from like a scientific or a biological perspective. So I wonder if, is it that these drugs are super effective or antibiotics are the best mechanism to get rid of these bacteria in the way that we traditionally think about them to say that one is the way that we think about bacteria? Is that the actual most effective means? Or is that actually how they work? Or do we not understand the pathways of how they're actually becoming more resistant to these technologies?

So my question, is there just like a group think in a way that we think about antibiotics and bacterial theory in biology or in medicine. We're just kind of following along the same path. So I would love to talk to a bacteriologist. And then 2, is this problem one that we will ever solve? Or will it just get exponentially worse? Because I can imagine, even if we come up with a faster and faster mechanism to get out these antibiotics and reach more people, will these bacteria just kind of keep growing and get faster and more resistant and we'll always have this problem?

And then thirdly, does that mean that we should have an established kind of entity within the FDA that just deals with antibiotics if they deem it as a serious enough problem and it's going to be persistent?



**AUDIENCE:** [INAUDIBLE]

**AUDIENCE:** Yeah, I can try to speak to that.

**AUDIENCE:** The question I was going to ask is you can about this theoretically. But I was going to ask, so if you had to start a company right and you're relatively young in your career and this might be a career-ender in terms of if there's no success, what incentives would incentivize you to start a company or solve this problem or an organization to work on this exactly?

**AUDIENCE:** Presuming you have the equipment and resources.

**AUDIENCE:** So antibiotics are pretty difficult, first of all, because they're becoming too effective for their own good. I think it was Pfizer or one of the big companies produce a very famous kind of antibiotic drug. And now, it's just so effective that they've kind of become a victim of their own success. And also, it's also really hard to pass antibiotic drugs through clinical trials, disproportionately so compared to other diseases. So that's also kind of like a barrier to entry.

I think, honestly, if I were to want to get into this field, you have to come up with a new approach, something better than is being done right now. Because I think antibiotics it's a very broad field. There's so many different strains. And if they mutate a bit your drug can be already rendered ineffective. So it's just one of those fields that is always evolving.

So not only do you have to have very strong basic science to keep up with what's happening with these bacteria, how are they like mutating, and how are they kind of evolving, and then you have to come up with drugs to help target them. So it's like a very twofold problem that you need to simultaneously target. And then obviously, they're evolving so rapidly that you have to kind of pivot very quickly. So I think it's one of those fast-changing fields that is kind of hard to target. But definitely important.

I'm not really sure what mechanisms they have in place or organization-wise to kind of target this specifically. But I think it definitely should be a focus.

**AUDIENCE:** You talked about your pipeline getting approved. What if they could speed that up very quickly so it's a priority?

**AUDIENCE:** I mean, speeding it up would help. But also, it's just hard to produce a good clinical trial for these drugs. So I think that's also a fundamental problem. It's just like psychiatric drugs. Those are very notoriously hard to prove because placebo effect is really a big problem.

**WILLIAM BONVILLIAN:** So that leads us right into our next reading, which is this FDA problem and the fact that we haven't put resources on the drug approval process. So Chloe, it's yours.

**AUDIENCE:** So if we're starting off with tackling that problem of how do we sort of reform and revamp the way in which we evaluate these products, one question for you guys would be-- so the meeting mentioned that one of the things you could attribute this mismatch was a mismatch between the levels of how far both research in basic science and applied science, where they put that. They're very mismatched in terms of one of them is just shot ahead and the other can't even keep up.

So what are your thoughts on how or if an agency such as the FDA should be responsible for ensuring the development of these sciences are evenly matched? For example, should the agency bottleneck the funding for basic sciences until applied sciences and catch up? Or should they aggressively stimulate opportunities on other side?

**AUDIENCE:** I suppose in an ideal scenario you just stimulate that's more funding to research drugs. But I understand that there isn't always money for that.

**AUDIENCE:** I forget-- but to that point, there is another reading. I forget if it was this one or not. But it said, just throwing money and giving infinite budgets isn't always the solution because, in that case, it takes away the element of good planning and strategic planning.

**WILLIAM BONVILLIAN:** The end of innovation organization. If you don't have the innovation organization, that's going to enable you to avoid big gaps in the system. You're just not going to get there. So throwing money at a problem without tackling the innovation organization problems is problematic.

**AUDIENCE:** Ideally, yes. Money in, money would--

**AUDIENCE:** Yeah, assuming that you can use the money properly. Yeah.

**AUDIENCE:** One thing that I was curious about. I was confused how antibiotics can simultaneously be working too well and you can have tons of antibiotic-resistant bacteria, which implies that antibiotics are not working too well. So if someone could clarify that, I would appreciate that.

**WILLIAM BONVILLIAN:** That's yours, Chris.

**AUDIENCE:** So I think the problem is that, say, Pfizer's drug is doing really well. So they give these

antibiotics to their patients. And these patients are getting cured. And so that means, if they're getting cured and they're not really getting these diseases, that means that drug is not going to be really used as much.

And then at the same time, because these patients have used the drug, there is antibiotic resistance growing. And just because it's been around for so long, it's inevitable that resistance is going to build up to the point that the drug is no longer effective. Because it's been out for 10, 15 years.

**AUDIENCE:** But that resistance can only develop if lots of people are using the drug--

**AUDIENCE:** I mean, obviously, a lot of people have used it. And it is, obviously, a critical mass have used it. It's been successful. It's a really effective drug. So maybe there's not repeat people in the way that other drugs might have a lot of repeat users. Maybe it's treating a large population, but people don't really get the same kind of strain of disease multiple times, something like that.

**WILLIAM BONVILLIAN:** And Chris, part of the problem is that we overprescribe antibiotics to an absurd extent. And we're sticking antibiotics in everything like hand soap. And we're virtually guaranteeing our own Darwinian dilemma.

**AUDIENCE:** It seems to be applying the language of this class in previous lectures. We're playing catch-up with an innovation problem instead of purely innovating, which doesn't seem like a very American way to tackle this problem. It's kind of odd because it's almost like we're being outplayed by nature, which, I mean, most of our big successes over the last 200 or 300 years have been us figuring out how to manipulate nature to our advantage. So it's kind of an interesting [INAUDIBLE].

**AUDIENCE:** I left my American flag at home.

**AUDIENCE:** If that's all we have for that, I do have one more question for the FDA reading, more on the standard setting sorts of things things. What do you guys think, again, are the roles and responsibilities of such an agency that sets these standards to encourage people to take risks and bring the slightly riskier drugs to market? Because the reading mentioned that a lot of researchers won't even go down that path because they know how arduous and tough [INAUDIBLE]. So is there something the FDA could do to--

**AUDIENCE:** I like what Bill said in terms of like, OK, it's a very hard process. But once you do it, you're kind of set. The only thing I would question is I would tier it. Because there's probably different

kinds of drugs that have different specialties. And they're probably something that-- there's pretty drugs that I really want to get tested really, really well. Or there's some that, even if I do test them, I still don't know and some drugs that can probably get passed faster.

So I would figure out like how does this scheme work. Look at the data in terms of how are these drugs being passed, how long does it take, which ones were relatively quick and see if I could restructure the organization so that I can optimize for the stuff that really matters and the stuff that doesn't really matter as much, it's not a focus. So we're having a linear kind of everything is the same.

**AUDIENCE:**

So are you saying maybe make the funding or whatever a function of, say, quality and the amount of time it would take to get passed so then, if you need a drug that maybe would only work for a few people, you can make it so it would be really high quality. Whereas if you have a drug that needs to work for a lot of people that you need really quickly, then you can make it so that it's less robust or for fewer restraints, et cetera, embracing something like that?

**AUDIENCE:**

Yeah, something like that. Because you also think about compound interest. So say I know that, if I make this drug, I'm going to save the government like \$50 million a year or \$80 million a year over four or five years. So if it's something that's going to make a big impact, how about we go faster and we can iterate faster? So we have priorities for drugs that really, really matter.

I don't like the argument of saying, oh, not a lot of people are going to use it so we're not going to prioritize it. And let's put it in the back because it's kind of false. Or maybe you should create another organization that only focuses on those kinds of drugs and split up the FDA into one that focuses on that so it gets equal review. But that's kind of a same wavelength.

**WILLIAM**

**BONVILLIAN:**

So just to kind of summarize here from your all good presentations and good questions, the FDA is sitting on a really critical part of the problem. So if we could significantly speed the drug approval process and if we could significantly lower its cost, we solve a lot of problems here.

We can be much less reliant on a blockbuster drug model. So it seems to me that, in terms of the panoply of fixes to this gap in the innovation system, really paying attention to how to accelerate-- Martine, as you were pointing out-- the review process at FDA. And it's very hard to reduce safety requirements. It's just not going to be acceptable to the public.

But if there are new ways of using big data and analytics and simulation and modeling, those

potentially present very significant improvements to this process here that could really help tackle this problem. So putting some money on that one I think could be really key. Then we go back to NIH, NIH is not organized around those kinds of technology problems. So how are we going to do this? So we have another dilemma as soon as we arrive at the answer. Anything else?

**AUDIENCE:** I mean, just as we transition into Bill's reading about this being a legacy sector or exhibiting a lot of legacy features, I'm curious about what you, Bill, or the class thought about the political viability of, I guess, in terms of Martine's proposal toward a tiered approach. If we thought it was more politically viable to do this for either therapeutic drugs or for cure-all interventions, there seems, in my very limited study of the life sciences, to be a proclivity towards the therapeutic drugs and interventions because they're more sustainable and profitable.

So do we think that that could be a potential market opportunity to test a DARPA-like system or to test the sort of improved speed of acceptance of the drug?

**WILLIAM** Let me throw that back to the group here.

**BONVILLIAN:**

**AUDIENCE:** I like the point-- I forgot when we mentioned it about how drugs were too low. So they want to have recurring revenue. But I think, as the government, you get a lot of, you have to pay that. So it would be interesting if the government is like, OK, well, we know, over the lifetime, if we don't solve this now, it's going to cost us one million dollars for this person.

So you solve it today, we're going to give you \$20k, which is way cheaper for us overall in the long term. But you're not getting paid \$10 per drug or \$100 per drug. And so it's kind of a win-win because it's really good revenue for the company and it justifies having a super drug that really, really works. And it gives them enough money on their balance sheet.

I don't know if you guys know how Warren Buffett got rich. But he got an insurance company. And they give him a lot of cash so that they can invest in other companies. And it's really good for companies having a lot of cash on hand.

**AUDIENCE:** Who'd have thought?

**AUDIENCE:** Well, no, it's just like a lot of them don't have a lot of cash on hand at any given time. So they have their assets distributed between physical. And so it's really good to be able to move

quickly and buy all this stuff. And it's just not a thing that happens that easily. There's also a lot of tax benefits. That's why people do it.