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Drawing The Line: The Ethics of Gene Editing | William Hurlbut & Rudolf Jaenisch

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The Veritas Forum

Stanford neurobiologist William Hurlbut and MIT genetic biologist Rudolf Jaenisch discuss the ethics of gene editing at a Veritas Forum from MIT, moderated by Cullen Buie, MIT professor.

Transcript

[Music] Welcome to the Veritas Forum podcast, a platform for conversations that matter and seeking truth together. We should never let ourselves get carried away by our ambitions and appetites and forget the profound needs there are at the very core of humanity.

[Music] We're thrilled to have tonight's conversation between Dr. William Hurlbut and Dr. Rudolf Jassenisch, moderated by Dr. Cullen Bui.

Dr. Hurlbut received his undergraduate and MD degrees from Stanford University. He then did postdoctoral work in theology and medical ethics. And since 1985, he has acted as a physician and consulting professor of neuroscience at Stanford.

During that time, his primary research interests have included the ethical issues related to biomedical technology advancement, including stem cell research, and the integration of theology and the philosophy of biology. Dr. Jassenisch received his MD from the University of Munich and he is currently a professor of biology here at MIT. In one area of his research, he uses induced pluripotent cells, stem cells to study the genetic basis of human diseases such as Parkinson's, Alzheimer's, autism, and cancer.

He is also a founding member of the Whitehead Institute for Biomedical Research, which is one of the world's leading centers for genomic research. Last but not least, Dr. Cullen Bui, who is serving as our moderator tonight, has received his MS and PH degrees from Stanford University, and today he is an associate professor of mechanical engineering. His research lives at the intersection of electrochemistry, electrokinetics, and

microfluidics, with applications in areas such as material sciences, microbiology, and energy storage.

Additionally, he is running a new startup company called Chi-To-Pen that is commercializing his lab's technology to make gene editing techniques like CRISPR faster. We are privileged to have these three people join us for tonight's Veritas Forum. I hope to see all of you at future gatherings exploring other facets of these issues, and I encourage you not to let this conversation end here.

Again, thank you all very much for coming tonight, and please join me in giving a warm welcome to our speakers. So, good evening. I'm very come here.

So what I understand is my role is here to give you a scientific basis of gene editing. So we know what we're talking about, and we're not talking about things which may be not quite reflecting the reality. So, let's put you on stage.

We have, we are composed of 22 pairs of chromosomes, 2 sex chromosomes, 6 billion base pairs. We have every thousand base pairs we have a mutation, most of those come from father and mother or mother, but we acquire mutations. And this leads to the variation between, for example, height.

So, we have chromosomes, our genomes and chromosomes, and eventually in DNA and eventually in these 6 billion bases. And if you, let's say, have here a C to T transition, C and T in two of the four bases, then let's say you're predestined to get Alzheimer's. If you have, let's say, this one, A to T, no phenotype, silent, and if you have this one, you get a cancer.

So genetics is really important for your phenotype. So the question we're going to be debating today is really, is it possible to correct such mutations and the potential to treat a disease? And should this be used in medicine and what would be the purpose? So these are the key questions I want to concentrate on. But we have to talk a little bit of the technology, because the key technology is gene targeting.

And I have to go a little bit in the history with two slides to put this in perspective. So the 80s homologous recombination was invented by Maricapecchi, where you have, I don't have a pointer, I'm afraid, where you have a piece of DNA like this one, which you want to insert into an endogenous gene. What you do is you build a vector which has homology in these blue here to the sides of where you want to insert it, and this then is a crossover which inserts the DNA into the endogenous gene.

Homologous recombination revolutionized biology in the 80s. And what you can do is, the event you're looking at is a very rare event. You have embryonic stem cells, and I assume you know what embryonic stem cells are.

They're pluripotent cells. They're really very important. You do your manipulation.

You get one, let's say, one in a million cells, which has the expected and desired modification. But you can clone these cells, clone, make a whole dish full of them, and now you want to make it most. What you do is you inject these cells into an early embryo, into a blastocyst, and then they can integrate in the embryo, contribute to all tissues, and make what's called chimeric mice, where the white is from the cells, from the modified cells, and this would be in a foster mother.

And then, if you're lucky, it contributes to the germline when you cross these two mice. So it's a way to convert a cell which is mute into an atom. So what is the issue here? Gene turning works very well in the cells, but only in the cells.

It's very inefficient. You need cells to find you a very rare event. And it's very time consuming.

This experiment takes if you're skilled one year, if you're not so skilled, more than two years. Long time. So the problem of causes for human-e.s cells, it doesn't work.

It works very inefficiently. And that was then the emergence of the CRISPR. So I will not go into the history of this.

I will just tell you with two slides what CRISPR is. So the age of CRISPR. It is the following.

You have an RNA, which is 20 base pairs long, which scans the genome for something momology and finds it. And this is associated with a protein. It's called Cas9.

And Cas9 is a nuclease. So when these two find their target, all what it does is it makes a double strain break in the DNA. That's all what CRISPR-Cas2 does.

A double-strain break. Okay? So there are two components. A guide RNA searches for the mology for your target gene and the Cas9 protein, which cleaves the DNA.

So it's basically a molecular scissor. And it really represents a revolution for biology and for medicine. And I will give you some examples for this.

And it even has an escaped Hollywood that this is something which could be useful for some story of terrorism or whatever. So CRISPR, you have the Cas9 component and then the RNA. And when it cleaves, you can insert a piece of DNA at the cleavage side.

It's reasonably efficient. Or if you don't give a vector, a template DNA, then you can make a mutation. Right? So this is the basics.

The question is, how efficient is that? I told you, a more logistic combination was very inefficient. You needed embryonic stem cells. How efficient is that? And that's something we were interested in.

I'll give you just a few examples. So when you take embryonic stem cells and want to ask

the question, how many genes can you target at the same time? With one, and we used in this case, five genes. And ask the question, how many we can do? And the result was 50% of the clones had all five genes mutated.

And both alleles. Incredibly efficient. We were really scratching our head.

But if you want to make a more sort of this, you have to go through this long period of injecting the cells and do a blastocyst, make a chimera, here, at least. So can you do it efficiently? That's a key experiment for what we're talking about today. So can we do it in the embryo itself? Just putting this into the fertilized egg.

So in this case, we put two guide RNAs for two genes. Plus Cas9. Into this, Emily, and ask the question, how many of the pups we get are mutant for the two genes.

And the result was a bit shocking. 80% of the pups had both alleles of both genes mutated. So we made the same imitation the old way in ES cells.

It took us two years. This took us exactly three weeks. The gestation period of the most.

But what you get there is really, you can't predict. You get some deletion, you don't know exactly how big it is. Can you make a defined point mutation? Exchange one base pair.

So we did the same guide RNAs, put them into the fertilized egg plus Cas9. Plus an oligo, small piece of DNA, 30 base pairs, along with, had one point, one base change. And ask the question, can we put this base change into the genes? Into the two genes.

And the answer was yes. 60% of the pups had this base pair change in the two genes. So this was amazingly efficient.

And this is the basis for what we're talking about. It's efficient. You don't need selection.

You don't need screening. It works. Okay.

So that's a -- so CRISPR, media gene targeting, germline, as I said, it's so efficient, it's rapid, three weeks. And you have the most. Because that's the gestation.

So now the question is useful for gene therapy or severe diseases, for example, as we discussed. So the applications of this technology is in disease modeling. So people can make not only mutant mice, but also, for example, monkeys.

So people have made no monkeys with a specific mutation which corresponds to major human disease, autism, for example, also. So there would be models much better than mice, of course, to work with. And it is already -- goes into clinical trials in combination with, as a targeted therapy for certain diseases like sickle cell anemia and whatever.

So it is already here. But what we're talking about today, should we use this, or at least what I think is most important issue, should we use this technology to alter the human germline? To manipulate human embryos. Okay.

So that's what we -- what I'm going to -- what I'm going to know address. So it's efficient, as I said. It's rapid.

The key thing, it doesn't need screening. It is so efficient that you can do it directly in the embryo. So it should be used to edit the human germline.

So what are the ways we can think about? Therapy, gene therapy, you can do it on a somatic level. Somatic therapy, correcting mutation, either in vivo of a patient, or ex vivo in bone marrow cells, which take out of the patient. The consequence of this manipulation are only for the patient.

The patient can give consent. German therapy, it's a correction of disease-causing mutation in germ cells in sperm, echombrial, which has consequences for the next generation. So I have a very nice example of that time.

I can talk about somatic therapy, but I think we'll concentrate on this part because that's probably the most interesting one for this discussion here. So why would you do that? And I give you three reasons. Correction of disease-causing mutation.

Inactivation of the gene, which makes you susceptible to some disease, or gives you resistant to some infection, or for enhancement. So let's say these are the three general areas one could think about. So I want to give you, now in the next three slides briefly, where the issues are, the problems in using that, as I can see it.

And I will first talk about the scientific issues. That's a basis. I'll later come to some other issues briefly.

So correction of disease-causing mutation. The complicating issues are, if you have a serious disease such as Huntington's, it's an awful disease, it's dominant. If you have this mutation, you get Huntington's disease.

There's nothing you can do. It's very terrible. So when you have a parent who is heterozygous one, 50% of his embryos will be mutant, 50% will be wild type.

There's no way for you to distinguish those two. There's no way. And that's principle.

Because there's one DNA and you want to modify the DNA. So therefore, you will manipulate 50% of wild type embryos. And I think that's a problem.

And you cannot, and I can go later into this, you cannot assess success because of mosaicism. I will not define this now. Disease-resistant genes, people think about, for example, you could inactivate the AIDS HIV receptor.

So you would have a baby and then a adult who is resistant to HIV infection. It's used in the clinic now for patients. So you could eliminate the virus infection, or you can correct other mutations to protect you against heart disease.

Now, one has to think about here. The alternative, of course, is you can do this also with the patient. So it's done in HIV patients.

They're corrected. You delete the receptor and they're becoming therapy. So you may not need germline requirement for the germline editing.

And finally, enhancement, for example, you can insert this pretty trivial insert the growth hormone gene into some expression locus. You will get a taller baby, but I think so that would be clear the expectation. And of course, this is scientifically feasible, but I think it's a different issue, which we have to discuss.

It's really much more post other than scientific issues. So one thing I want to say, these are the scientific issues which I think argue against editing in zygotes, because you can't assess what you did. You cannot.

So it has to be so efficient that you can do it, but biology is never that efficient. But can you overcome that? That's getting interesting now. If you do it post-nately, can you do it in spheromadoboneal stem cells or oocyte stem cells? The advantages, those cells can be cloned, and you can assess what you did.

And I'll give you the example. This is a study from Ralph Brinster in the '90s. So he isolates from testes, spheromadoboneal stem cells.

They can grow in a culture dish. And when you put them into a test, they can make sperm, and you can see the blue mice that can give rice to offspring. The key is, since you can clone these cells, you can manipulate them, have a sister clone, and evaluate whether it was right or not.

That would solve the scientific issues. And there's also the idea that you can do this possibly with making oocytes from stem cells, from pluripotent stem cells, oocyte stem cells. So you could do this also with female cells.

So the use of these type of cells would resolve, may resolve, these scientific issues I erased. So note becomes more interesting. If you would have resolved these scientific issues, should you do it? So, and I give you just a few thoughts about it.

I'm sure that Bill will much more go into this. So the ethical worries would be mistargeting causes uncertainly or unwanted problems, spectra, eugenics, slippery slope to eugenics. Once in the use, you cannot really, may not reverse it.

Editing may access where inequality and so on and so forth. Arguments against germ

manipulation would be intergenerational content is not feasible, impossible to predict consequences, and the threat to human dignity. The counter-arguments would be intergenerational concept is not relevant for multiple other decisions regarding future decisions.

We, that our next generation grew up in a climate change world, right? We don't ask them. So I think that's one, the counter-argument, impossible to predict the consequence for other well-intentioned efforts to improve human conditions. All the time you have that.

And I think there's no shared conceptions, these far against the regarding the notion of human dignity. So I think this is a debate which is ongoing. And let me just say, I was on the committee from the National Academy of Science, which worked out some guidance for germline editing.

And as the book was published last year, and I'll give you a few highlights of this, and I think Bill will much more go into this. So they say, yes, it should be absent of any other alternative than you might consider that. The restriction is really you have to be convincingly have the science done.

Very good, good science, basically the same. Maximum transparency, it's really absolutely clear about it, should be, and reliable oversight. So this is just a very simple summary.

So let me come to my final slide. So why should you do this? Well, disease prevention, TASACs, hunting this, I mentioned, sickle cell, that could be eliminated these disease genes from the next generation. But you should consider the alternatives.

I mean, you can, if you don't want to hunt any of this baby, if you could make pre-implantation genetic diagnosis and select the embryo, which doesn't have the mutation. Very safe. And it's in use in the clinic.

And somatic therapy, as I said. But there, some, there may be no alternative whatsoever. Because for example, if you're homozygous, if the parents are homozygous for, let's say, hunting this, or both parents are homozygous, for a recessive disease, there's no way they can have a genetically normal child.

So this might be the only possibility. And if there's infertility with this, why chromosome linked would be similar. So that's disease prevention, modifying disease risk screens.

So, could you, as I said, could you make babies who would be resistant to virus infection by inactivating the HIV receptor? Trivial, scientifically. All the other genes to affect your incidence of Alzheimer's, Alzheimer's, or heart disease, or cancer. Enhancement, should you do more muscle in the offspring, eye color, learning memory.

And of course, these are very complex traits. So these are the issues you can consider. And I think the point which we probably today discuss, what is permissible, what's not permissible.

This is not, obviously not a scientific issue. That's something which society would have to decide. And I think I let Bill follow this.

So that was a very good introductory framing of the science. I want to talk with you about the ethical, the social and sort of personal issues of this. This is an extremely important issue.

I can't tell you how significant I think this is. And I think what Moody's told you already confirms that. About a year ago, Dr. Inish and I were on both speakers at a conference at Harvard.

And this was the poster. And I thought it was an interesting way to start to reflect on human hands, what Aristotle called the tool of tools. The symbol of our distinctive body form and our unique capacities of mind are comprehensive, creative and controlling capacities as human beings.

Really, we're remarkable species. These hands are now reaching into the most fundamental forces of living nature. And that raises enormous problems.

70 years ago, all this Huxley anticipating the transformation of human life through advances in biology as the final and most searching revolution asserted this really revolutionary revolution is to be achieved not in the external world, but in the soul and flesh of human beings. Now, in what MIT Tech Review has called the biggest bio-tech discovery of the century, we have a tool that is finally after about 50 years of doing this kind of science. It's very precise, very inexpensive and very quick to do.

So, there's a right at the edge of a major revolution in biotechnology. It's been characterized, and Rudy showed this, so it's been characterized as a molecular scalpel, but in fact it's really more like a Swiss army knife. It's gotten multiple ways of intervening at all levels of genomic process.

Together with our exponential increase in gene sequencing capacities, our deepening knowledge of genetics, cytology and developmental biology, the scope and versatility of this technology promises transformational impact as great, I think we'll see in retrospect as great as the discoveries in electricity, synthetic chemistry in the end of the 19th century and then nuclear physics in the early 20th century. This is a dramatic moment, I believe. Physics, chemistry and now biology, biotechnology, full circle on the enlightenment dream of mastery and as masters and possessors of nature.

We may be finally approaching the revolution anticipated by Huxley and with it a huge profound and vexing questions about our aims and our applications of this and the role

within the human role within the natural order and the proper use of this technology and shaping the human future. At the most fundamental level, these questions go beyond issues of individual rights and social responsibilities to considerations of the very source and significance of the natural world. It's integrated and interdependent processes and the way these provide the foundational frame for human existence, human identity, because it's not just medical issues are going to be addressed.

We're potentially going to transform vast swaths of the natural world. The largest lens of these considerations is the natural and social environment that sets the frame for the physical, psychological and moral and spiritual meaning of human life. In other words, we're about to transform the world of living creatures the way we have largely done with the inanimate world around us.

It's a very, very remarkable moment. Is the natural world simply a coincidence within a chaos, an aimless and arbitrary product of physiochemical processes, or is it a moral and spiritual order requiring humility in a sense of limited human prerogative of rights and responsibilities that we have to take seriously? Proposals for the use of CRISPR and other gene editing technologies range from the fascinating to the frivolous projects of broad ecological engineering. The extinction of human ancestral species have been proposed.

Recombinant actions on animals. We already have a bunny that glows in the dark. That probably didn't hurt the bunny at all, but it's just a foster and gene.

But you can imagine with this technology, you might really get pretty wild. Who has rights about that? Do the commercial developers have absolute rights or is there something about human role over the animal creation that we ought to take seriously? Likewise, there are serious proposals for chimera creatures. This is really a joke, but think about the way creatures could be blended and genes could be blended between species.

And then, of course, there's visions of the human future, including engineering the perfect astronaut, treating aging as though it's a disease and therefore reversing it or countering it somehow. There's the astronaut picture. And then there's the transhumanists.

Some argue that it's human destiny. It's human nature to just go forward in this kind of technology to improve ourselves even at the most fundamental levels of our genes. These include, especially the transhumanists.

I'm sure you have transhumans here at MIT. They're an international intellectual and cultural movement, advocating technologically mediated enhancement of human intellectual, physical and psychological capacities. Their logo is H+.

It's human with a plus. I've had several of the leaders of the Stanford Transhumanist

Society in my classes. They're intelligent, serious-minded students.

They argue that our advancing technology offers us the opportunity to escape the constraints and cruelties of an amoral evolutionary process. And the opportunity to lift humanity in its next level of personal and social flourishing to enhancement of human machine hybrids to the creation of post-humans, they argue. Others with more modest goals, there are some who suggest we just simply use it to make ourselves smaller so we don't consume so much resource in the world, but I think that's really a joke.

But others with more modest goals point to the very serious role of these technologies in addressing disease, doing biomedical research. And the final issue that's overarching, all of those, is a question of our vision of nature, what's nature for and what's the right thing to do. So I just want to take a quick, way too quick, tour of what the human dimension of what Rudy has laid out.

This is Jennifer Doudna, who is one of the discoveries of CRISPR-Cas9. Jennifer and I are working on a project together on the social and ethical issues implied by these advances. And Dr. Ganesch is part of our working group, very important issues, I think, issues for the best scientists, scholars, and thinkers in the world, but also for the whole human family, because these are species issues.

They're not issues for elite, educated people, only they're issues for the whole human family, the people who do the perennial tasks of having the children and the work a day tasks of life. But we all know that fundamental moral imperative of human life is to treat disease, in this case, sickle cell anemia. There's now proposals for taking the cells out, the stem cells out, modifying them and returning them into the bloodstream to repopulate the marrow.

A hopeful process, who I think is likely to be effective in the next few years. There's even ways of sending these vectors carrying this agents that Rudy talked about using viruses or nanoparticles, gold nanoparticles are the latest thing, liposomes. There's ways of delivering them internally to the body, harder, but maybe feasible.

And then so we get to the point where we ask ourselves, "What about it? What's the right thing to do?" And as Dr. Ganesch pointed out, there's somatic cell interventions and germline interventions. But at either level, we can feel the imperative, this poor little fellow, and this is a disease called Lesch-Nihance disease for the children, actually chew their fingers off. And you're experiencing a certain metabolic factor, and it's very terrible, and you feel the weight of this.

But what's right to do, and how much risk, and is it really right for us to start engineering the human genome? And then you ask yourself, "Well, where will it go?" It's not just very serious diseases, but what we might think of as "quazy conditions." This is albinism. Is it really a disease or a human variation? Well, you could argue that there's deficiencies

with it, but people live very good lives with albinism, too. And then it blend over the obvious issues of parental preferences, and eye color, height, and so forth.

Not going to be easy to do, by the way, any of that. But still, it raises issues of enhancement, and when you start to think about all the things that are genetically grounded, it really raises a lot of possibilities. Although, let's not be so foolish as to think genes control everything, because even identical twins are not all that similar when you get down to the actual processes of their biology.

So, what would we do? Well, are there good intermediate things to do? This is George Church from Harvard. George has identified what he calls "rare protective alleles." These are dimensions of human, found in the human gene pool, that are variants with large impact that exist naturally, but they're not as common as they could be, and maybe beneficial if more people had them. They're the whole range of these, and George has suggested that we might want to improve the human stock by doing that.

There's a whole bunch of them with significant things. Of course, number four is variant of low odor. I'm not quite sure what that's about, but in any case, maybe that would be the most popular.

I don't know. But it does raise challenging questions as to whether it's our role as human beings to improve the human gene pool. But other people, like developmental biologists, Stuart Newman warned that the genetic design of future offspring, even limited objectives, make it difficult because there are different definitions of normality, different access technologies, and different willingness to take risks with future lives, which is a serious bunch of considerations.

But while where I come from, and I'm sure it's right here too, there's a spirit of innovation and quest and discovery, so there's a lot of momentum behind the idea of improving human beings. And yet if we go back a ways into the history of our species, we realize that there's a long history of considering what the role of human beings is in their own interventions against disease. The Roman physician, Gail, said that the physician is only nature's assistant.

But now look at what we are considering doing. Now with the powers of our advancing technology, there is new paradigm, one of liberation, technological transformation in the quest for happiness and human perfection. Grounded in the widespread practice and general acceptance now of cosmetic surgery and other lifestyle interventions by using pharmaceuticals, slowly but steadily the scope and purpose of medicine are being extended along the gradient of our appetites and ambitions to encompass dimensions of life, not previously considered matters of health, but natural human variations.

And that raises a very profound question. I mean look at the things we've done, growth hormone, those people were not really, they don't exactly have a disease, they function

well, but they're not socially the right size. And then people have accepted birth control pills, Viagra, lots of interventions.

We're getting to the point where we're trying to remake our lives. And when you think about it, who wouldn't want to have certain advantages in life and certain advantages for their own children? So their proposals for better brains, including by the way, proposals for intervening and genetics in a way that would produce more moral human beings. I'm not so sure that's even possible, but it's been proposed, advocated.

And of course there's quite a thrust in California, Google has the Calico, the California Life Institute, working on longevity interventions. And I was at a conference where William Hazleton said the real goal of biotechnology is to keep people alive forever. And it's natural, human beings want perfection, they want for themselves and their children.

So this is a huge temptation. When I served on the President's Council on Bioethics, we produced this volume that examined these issues and looked into the underlying questions, and it was not easy to define the difference between therapy and enhancement. This, for example, was considered a therapy at the time of the Civil War in the Antebellum South.

This was a defined disease in the textbooks. It was called Dreypetomania from the Greek words "attendency to run away", a passion to run away. And you can see his treatment as a slave was to be whipped.

And of course we all know the sad history of Nazi Germany, which was trying to aim for perfection, but ended up terribly tragically. So it's not easy to define a disease, and it's not easy to tell people what they shouldn't do, because everybody knows about Lance Armstrong. And so we have a precedent for this.

And I'm not trying to exaggerate this, it's going to be difficult, but it actually is no longer a completely science fiction. They were moving into the realm of technologically altered human life, raises profound questions, and those questions were raised and addressed initially through Jennifer Doudna's concerns. There was a gene editing summit that Rudy referenced, and they were taken seriously.

But at the same time they pointed out that to address complex diseases like cancer, we must carry our investigations in the most fundamental elements of living systems, which brings us to the most profound questions, besides the modification of human embryos for therapy, it's obvious use of modification of human embryos for inquiring into the very nature of developmental biology. So before we had these multiple embryos, and there was controversy over the development of embryonic stem cells, but now there's a vast new arena of possibilities for the use of embryos to study specific disease mutations in embryos to produce embryonic stem cells that could serve as models. So now the tools are in place for vast increases of valuable science for sure, but controversial science.

So remember when the stem cell issue was a, our country was divided deeply about this, and in my own medical school had a, the cover of our Alumni magazine pitted science against religion. That was a false dichotomy. There were many people on both sides who were religious or against embryonic destruction for non-religious reasons.

But both sides had their arguments. Good science could come. On the other hand, there was the defense of human life as living human organism from its initiation to the end of its natural life with death.

This is an eight cell human embryo on the tip of a pin. And the argument was, well, human beings at all phases of life are developing individual organism. There's a continuity of being, and that therefore we should defend human embryos as a sanctity we give to normal human life at other stages.

This was a very, very difficult controversy that we all worked through sort of, but never really resolved. But it did leave us with what I want to address as the final issue here. If, in this age, there are many uses we could make of human embryos with this new, new technology.

And we're going to have to decide what our principles are. I just want to raise four questions. Will we now endorse the use of human embryos for a wide range of studies of infertility and early development, not just for getting stem cells? There are many, many ways to do this, and many useful experiments could be done.

Second, will we allow the creation of embryos specifically for research purposes? They do allow that in the UK, by the way. And that, I had that in there from past lectures, so I thought I'd leave it. That's Dr. Yanish.

Is that the very mouse, Rudy, that was created? He made the first transgenic mouse. In this case, he was telling me at dinner. He wasn't exactly a study of developmental biology, but you can see how if you could knock genes and knock genes out.

We could study human embryos and understand human development the way we studied mice for the last 30 years. So, there's no doubt that the science could be very useful. The question is how about the ethics? And if we do this, how many embryos would it be okay to use in research? Well, a Japanese scientist created 581 copies through rounds of cloning.

And whether it's cloning or some other method, creating batches of identical embryos and doing controlled studies would be a very useful scientific enterprise. How would we get the cells to make those embryos? As Dr. Yanish pointed out, we're getting the point of harvesting them through in vitro production from induced pluripotent stem cells. But there might be other ways, too.

15 years ago, a stem cell biologist and Dawa Salter raised this issue. He said, "You could

have millions of gametes. You could combine them." And today we can't do those experiments on human embryos because it's considered morally repugnant.

They're difficult to get. But if embryos could be grown in culture like any other cell line, this latter problem would disappear. They'd be easy to get.

They'd become like any other cell type. They would become objects and would be used as objects. And then he went on to say, "I have no idea what kind of moral value or rights we would give these embryos.

We'll probably go through the same agonizing we did with IVF. It could be terribly difficult to begin with, but then would become a fact of life. 20, 30 years from now, we might read in the papers, somebody made 20,000 embryos, studied their development, and we'll decide it's okay." So you can see huge issues.

And then, of course, the very, very difficult one is, will we allow research on embryos beyond 14 days? And if so, for how long? And according to what principles of moral valuations in the United Kingdom, they allow embryo research up to 14 days. But now that they can actually keep them alive longer than 14, there's a huge controversy going on about whether they should revise that rule and allow it to go on. There was just an article in Nature Biotechnology two months ago about this big debate going on.

And this scientist at the Francis Crick Institute is already doing studies of developmental biology with human embryos. So there's going to be a big controversy over this, probably an international controversy, and it's going to be difficult. Now, would anybody really want to go beyond 14 days? Well, my colleague at Stanford was on the California State Commission on Human Cloning, and somebody asked him why they drew the line at 14 days.

And he said, "Oh, that's just the first limit, just so people get used to it." And we could change our ideas about how long in the future based on likely changes of their understanding of neuroscience. What was neuroscience have to do with it? And, of course, what's gravitating slowly but surely is the notion that you're a human being, and only when you're conscious, self-reflective, and so forth. I'm raising this for it because this is going to be another very difficult debate.

And would anybody do this? Well, I debated this guy, Julian Salvalescu, some years ago, out of form in New York City, and he said that not only would it be okay to do it, we haven't morally required to produce clones, implant them, and harvest them for the cells, tissues, or even organs. I asked him, "How long would you let it just stay before you harvest?" This guy's a physician, by the way, and a head of a bioethics think tank at Oxford. And he said, "Six months?" He said, "Yes, I'd go six months." So there's going to be controversy.

And Erwin Shargoff, who was a major figure in early genetic technologies, was warned us that we were going to have to face these profound questions as biotechnology advances. And it was warned us that the time was coming when there would be useful cells, tissues, and possibly even organs could be extracted from human beings, early human beings, like we'd currently take, like at one point they extracted gold teeth. So I don't want to sound pessimistic about that.

I don't know any scientists that have terrible scenarios except for a few that are like that guy, Julian Salvalescu. But nonetheless, there are different cultures and different nations. And I gave a talk in China a year ago at the 60th anniversary of Renman University, which is the original Communist University.

And I was talking about these kind of issues. And afterwards, the chief ethicist, bioethicist, China came up to me and he said, "You know, he was commentated. He came up and was commenting in front of the audience.

He said, "You know, in China, we don't believe you're a human being until birth, and therefore those kind of projects would be okay." And so he said, "Confucius says you're not a human being until birth. Afterwards, a philosophy professor told me Confucius does not say that. But be that as it may, we've got difficult international issues to contend with.

So what is the connection between human beings? It's the only slide I can find as a man, but it's obviously humanity. What are our roles? What's our prerogative? How can we engage the people who do the normal human life that don't necessarily have scientific perspectives, but have strong and beautiful opinions about what's good and true in life? People who work hard, sacrifice for their children and hold our society together. They need to be engaged.

So I just want to end with a picture of hands again. What is our place as human beings? Obviously, this is from the Sistine Chapel, and it raises a profound question of what are we? Are we co-creators in the world? And if so, in what sense do we operate in the realm of both science and spiritual truth to do the good that we are capable of understanding? A profound creation we're part of. It's mysteriously beautiful and horrifying at once.

There's tragic disease, but there's also very moving dimensions of evident beauty goodness in the natural world. So how do we find this mysterious balance and how do we go forward in a way that is humble? The very word humanity comes from the same root as the Latin word humus, earth or soil, and therefore it's the same root also, the word human. So human beings should be humble.

We're creatures of the earth. We're formed in fashion by the earth and we have to be humble as we dwell in it. And we should never let ourselves for sure.

We should never let ourselves get carried away by our ambitions and appetites and forget the profound needs there are at the very core of humanity. Thank you very much. Alright, so thanks so much for both of you for your words.

And I think one thing that stood out to me was there were some words that come up that are difficult, that are kind of germane to this discussion, that are difficult to define, things like good and severe and disease. And I think before we dive in a little bit further, a question I have for you is kind of what is your, when I think of like what is a good life? What constitutes a good life? I think to define what is a good life, you have to know, well what is your world view? What defines a good life? And so I'd love to hear both of you talk about your view of the world, perhaps faith, religion or otherwise, and how that influences your, if at all, how you think about these topics. Colin, my world view is that of a practicing Christian.

I was not raised in a religious family. I was kind of a radical student in the late 60s at Stanford. And then I became dissatisfied, dissatisfied and frustrated by what was going on in the culture I was part of.

And I went back to my room and I had a Bible I had been given because my parents forced me out the door to Sunday school. I didn't want to go, but they didn't go. So I had a Bible that had been given to me as when I was confirmed.

And I didn't know, I really didn't understand the first thing about it, but I decided I'd read it. And I think maybe I was okay with it because I remember Jesus had long hair. So, you know, that was the 60s.

I don't know if that was in there. That wasn't in there. They might have been the pictures.

Yeah, that's like that joke about the kid that goes to the father and says, "I want a car." And his father said, "Okay, you get straight A's. You read the Bible every day and you cut your hair." This is the 60s, you know, long hair and the parents didn't like it. So, six months later he comes back and he says, "Okay, Dad, here's my bread port card straight A's." And I read the Bible every day.

And his father said, "Where's my car?" And his father said, "Well, what about your hair?" And he said, "Well, Jesus had long hair." And his father said, "Well, Jesus walked." So, I became a Christian reading the Bible and it shaped my life profoundly. I don't claim any single denominational emphasis. I don't understand the arguments well enough.

But I do define my sense of truth and goodness around the life of Jesus. And I don't just mean ethically. I mean in the very deepest sense that I believe that in the higher cosmology implied by the phenomenon of the created order and the destiny of the created order that's spoken of there.

So, that shapes my life. It is not, however, the only input. I use my scientific thinking and my logic as a human being, drawing on just plain reason, to try and think through where some things are beneficial and good.

And so, it's a worldview that's grounded in a certain spiritual metaphysics, but also in just normal living and human understanding. Okay. Well, okay.

It's very different. I was baptized, but I left the church as soon as I could make my own decision. For me, the important thing is I want to find the truth of the world.

And the concept of God is not, doesn't help me to do that. So therefore, I do not believe in something like what many of you do. And I don't think this affects my being ethical or being not a bad person or whatever you want to define it.

It's not relevant for me to have that as an important background to do that. So, we can talk about this. Why this is, but maybe that's not the right thing here to do, but what I think, and you asked me that question before, why do we want to talk about ethics of science? Let's say we go back to all the theme.

I think the science we have now, and we talked this evening about this, is in contrast to the science I did 20 or 30 years ago, which was very far away from any application. You would write in your grant application that all has importance for human diseases. I never believed that.

I think it was just a phrase, but now I believe it. It's very close. So obviously, you have no obligation to really be transparent, to know, to tell people that's what's going to happen if you do that.

And so I think there's an obligation, anyone who works in science has to be transparent and to be informing people, and certainly Bill and I have done this in some occasions. The question, what should you do as scientists when you design an experiment? If the experiment could have bad consequences, should you not do it? If it's fundamental research? And I believe this is not the right approach. You cannot forbid people to think and to explore.

I think that to me is almost under you. Everything can be misused, everything can be used in the right way. I think where the border is, and it's a very strong one, when you apply it to human beings, to medicine.

This is not a scientific basis to this, but it's a different type of decision. And I think that's where, very clearly, the border, this is a decision we as society, we as human beings have to make. Do we want that? Or do we not want that? We will be very, there will be very many different opinions, and you voice some of those.

The trans humans and people who I was being on this committee from the National

Academy of Science, for me, it was a very strange realization that people who are deaf don't consider this as being a handicap, but as being a culture, a cultural trait. So they won't get deaf children. There was this case where this couple looked for sperm donors who had a high chance to give them a deaf child.

Now you see they're very far away views on how to use this technology. So I think that's what we'll have to figure out how we come to a consensus, if there's a consensus possible. Maybe this discussion is an attempt to do that.

What do you think of that, really creating a child intentionally deaf? I think it's totally, to me it's crazy, it's totally unacceptable. Of course, as Anwan can ask the question, can you make decisions on the next generation, as we said, when you edit and change in human embryo for whatever reason, it's a decision you make of someone who can't give a consent. So you have to think about that.

So I think there's very complex questions, which I'm unable to answer. I have an opinion of those, but I can't answer them. So you mentioned drawing a line at when these technologies affect humans.

Yes. And Bill, in your talk you discussed, there's differing views on when does human life start. And so I guess I'm curious, and hearing you guys discuss a little bit around that issue.

So when is, when do we have a human? When do we go from cells to a human? So I can give you, when human life starts as a biologist, there's no other answer than with fertilization, then life starts. I mean, this is not the question, which is interesting. When do you consider a human embryo as being, being worth to be protected, being protected against whatever? That's, I think, the key question, not when life starts.

I find this wrong question. Fertilization, what else can you say? But this doesn't mean that the fertilized egg is untouchable. To me that is, and I think the compromises we have made, the burdens have made as a first country, that you can use fertilized human embryos to make embryonic stem cells.

And you can fully support the clear cut restriction they had. So that was after life began. Of course, you had an embryonic stem cell.

You had a blastocyst, which after seven days put in a culture dish, you make an embryonic stem cells. So I have, I find this the right decision, the British did first. And we have done it, my laboratory we have generated human embryonic stem cells under the right conditions.

I don't see this as something which I find problematic for me. What's your question? Let me just ask you about that. How do you feel about the controversy in England to carry it beyond 14 days? So I think I would differentiate a lot.

If it's 14 days beyond implantation, right? So the British made a very clear rule. You can do something with a cleavage embryo, with an embryo which grows on a culture dish up to 14 days. And then you have to make an embryonic stem cells.

But once the embryo is implanted, so implantation is a red line. Once it's implanted, you can't touch it. And I would think that is really a good line because there's no gray zone.

Either you implant or you don't implant. There's not nothing half, right? Now comes a problem with embryos, human embryos being grown in a culture dish beyond 14 days. And there's no experiments published.

You can use embryonic stem cells or mouse embryos, but you can grow in a culture dish up to the primitive streak stage. So when they do get an axis, have symmetry and get a beating heart, that can be done without outside of the uterus. So this is of course a very new development.

So this line, the British line, might eventually be getting a little more fuzzy, right? I agree with that. You can make these human embryos embryo-like constructs from embryonic stem cells, which of course it doesn't involve an embryo, but you get an embryo-like structure in culture. Now is that different for me make the same structure for my embryo than for my embryonic stem cells? I wonder.

So these are, I think, interesting issues. For me, manipulation of an embryo in utero, for whatever reason, if it's therapeutic, I would support it. If it is for research or for manipulating, I think it's a really very complex and I would have a lot of hesitation.

So if you could develop an artificial endometrium in a lab and implant the embryo and grow it to 20 or 30 days, would it be a little bit of a razor spray? Yeah. Very complex issues. So one thing I didn't put in my presentation because I already talked too long, but George Church at Harvard has published a paper on what he called "Sheaves, Synthetic Human-like Entities, Embraerial-like Entities".

And he says that the 14-day rule was interesting when it was just going from the beginning and working up through natural development. But now with the new tools of developmental biology you can create later cell types, join them and they self-organized to the level that he can actually get cerebral tissues and brain tissues. And he's asking the question which doesn't really have an easy answer, when does this have some kind of intrinsic dignity? Because most people do believe that what endows human life with dignity has to do with something to do with our neurologic system, obviously.

And the question is, well, could we create anything in the dish even if we didn't come up from the bottom but just bypass the early stages and create partial human-like DNA? And I'm going to say that's, I doubt that a cerebral organoid, that's what they call them, just brain tissue would have any kind of consciousness. I've done it seem true to make

your biology to me, but nonetheless it does raise profound questions because we don't actually know what consciousness is. And if you're honest about it, nobody knows.

We don't know what it rises in, most of us in science suspected it's a molecular-immediated phenomenon at the very least. And yet we don't know the minimum construction of it. And so we're looking at a very, very complex future dilemmas from all this.

And I think, I agree, we're organoids, you go on a culture they will never think, right, these mini brains or whatever they agree. But I think it's interesting to do this in vivo, make chimeras. So make human most chimeras, which we're doing for a certain question because we want to study human disease in a vivo context.

I don't have any problem with this because it will be never human. But you go on, if you make human monkey chimeras, it gets very complex, right, that's something I think will not be allowed. Because then you don't know what you have because there will be the integration of the human cells will be high and mouse that's very low.

And so there's two evolutionary, two distant monkeys that close. So what is it? Something between the human and monkey? So then I think it's a, you cross the line. And I don't think this will be allowed.

But I think one challenge is the line differs for everyone. And I think even if we were to discuss for hours, we probably may not come to a consensus on where lines are. But one line I'm curious in is how would you both define medical use of therapy versus enhancement.

So for example, you mentioned the example earlier of a couple that was deaf and was interested in having a child that was also deaf. And that might sound crazy to us, but that's really our opinion. And is our opinion any more valid than that couple's opinion in a decision like that? So how do we come to consensus on these challenging issues when people can have different opinions on what is valuable and what is good? So I think if you make a AIDS HIV resistant baby, this is a form of enhancement, right? You could argue.

Should you do this or not? And I would think you don't know what you're doing because this receptor for the virus is they're puttically inactivated and cures people. So that's in clinical trials. This receptor also is another function.

So what's not known that much? If you don't have this receptor, you're getting more susceptible to infection with another virus, corona virus. So that's something which you have to consider. You don't know what you're doing.

Another suggestion was could we eliminate the apo-E4 allele, which is the most strongest risk factor for Alzheimer's? And it's pretty prevalent. So if you have apo-E4, your risk for Alzheimer goes up 34 or something. So it's really pretty bad.

Should we eliminate this by editing this apo-E4? It's one amino acid change to make it for apo-A3 and apo-A2, which is the protective alleles. Should you do that? And so eliminate this terrible gene from the population. But I have just recently learned this.

It's interesting. There's a tribe in South America. They have very high incidence of apo-E4 allele.

40, 50% have the apo-E4 allele. Why? Because it's a selective advantage. Because they're more resistant to some parasite that what people believe.

So what you do is these type of things, we have this diversity in our population to respond to changing environmental challenges. You talked about sickle cell. It's a big one pretty.

There's sickle cell and of course the malaria. So sickle cell, of course, this mutation protects against malaria. If you're heterozygous, homozygous, you're very sick.

So surely this is a terrible disease, but the test selective advantage. That's why this mutation is so prevalent in Africans. Yeah.

So a couple points about, as I said in my presentation, we studied this matter of the difference between enhancement, therapy and enhancement. And it's not an easy distinction for a variety of reasons. And if you're interested in it, I'd suggest you look into that book Beyond Therapy.

It's actually, I think, the best thing we did as a council and quite thoughtful, really. But let me just throw out a few things, just the crazy scientific, but I think bear on the discussion. First of all, I mentioned designer babies, and I didn't say it, but there's also proposals and have been in the past for state run eugenics programs.

I wouldn't dismiss human cultures that are in the modern world, that might go for that. I've talked to some scientists from Asia who say that their culture would be open to that. But I think we should get it out and make it clearer.

None of these large-scale enhancements are going to be easy to do. I think it's a myth that we're right on the cusp of significant designer babies. It's one thing maybe to change to alter a gene for susceptibility to HIV or up a week or something.

But the idea, what do people really want to do? They make more beautiful babies, more intelligent babies, babies that will live longer life. All those qualities in human nature are controlled by hundreds, maybe thousands of genes. And so far, for the most part, they're very little that you could intervene in with a single or even a small cluster of genes that would make a very large-scale difference in that.

And beyond that, we only know that certain genes work in certain contexts of other

genes, and those genes will get re-asorted, reshuffled with each generation. So in terms of making designer babies in a superior culture, that's not going to be an easy job. You agree with that, Rudy? And the primary reason is because of two basic principles.

I tell my students, "You've got to learn these. If you learn nothing else from me." The concepts of polygenic inheritance and plyotropy, those two words that have big meaning in biology. One is that most traits are controlled by many genes, as I just said, and most genes affect many traits.

So if you're going to go for something that you think this one gene is going to contribute a lot to, you're going to get a lot of other things you didn't bargain for. And that's why single-gen genetic diseases often present medically as syndromes. The person might have eyes too far apart, their web feet, they might have a heart defect.

All these things, because the single little tiny protein in the middle of it all is affecting many things. So I don't think these large-scale scenarios are very realistic in the current world, and probably may never be. So what we do about intermediate kinds of enhancement and private choice, as you say, who's right, is it to decide? Well, I think there's some general principles we ought to not necessarily enforce, but take into our culture so that some of these things are not necessarily illegal but unthinkable.

And one of the problems we face as a modern world is that because historically we've had our cultures and we've had our traditions, and they have been who we are. The very word ethics comes in the same root in Indo-European as ethnic. We are who we are because we are those people.

And often, by the way, associated with the land they'd well on too. So ethics wasn't controversial the way it is in our modern world, and that's partly because of the advances of technology, but also because of the convergence of people from all over the world. And so we've sort of reduced in our society to the lowest common denominator for ethics, and that is don't impose suffering on other people.

And suffering is sort of the greatest evil. But I think we have to be a little careful because the argument from suffering can be used to justify almost anything. There's more in the equation of human life than to combat simply and directly against suffering.

Now I'm a doctor, I'm none favor of suffering, and I'm not worshipping nature in the sense that I think nature is the perfect paradigm to be left alone. It's just that what we do in medicine, at least in good medicine, takes account of the whole person and the whole culture they're part of. And there are things that you could do that would relieve suffering that would in fact be, they would be evil actually.

And I'm not in favor of those because I think the ends are not the only goal, the means to those ends also count for something. And that perspective honors human dignity in the

process. I mean if we said to the MIT undergraduate population, you know we just need just a couple of you to test this drug on, and what are your lives compared to the thousands of people that could help? Nobody would say, oh that's okay.

We have to be careful before we think that way about developing human life as well. I'm personally not, I never really answered the question on embryo research, but I have big qualms about the use of human embryos in research. I think for both reasons of principle and reasons of prudence, I don't think it has a natural stopping point.

Like I said in my presentation, one of my colleagues says that the definition of human life will eventually come through neuroscience, but if we really put Rudy to the test to have a hard time saying when he thought human life had dignity, right Rudy? Yeah, what's a complex question? And so what happens is, you know, one person gets off the train at one station, but somebody else goes on and they say, "Well, that's your private culture that you got off earlier, but you know, I'm in favor of relieving suffering by studying not just embryos but fetuses." And I mean most people would find that, I think in the current world, find that abhorrent, but maybe not everybody. And then who gets to decide? Why can't they do research on, why can't that guy, apart from the practical barriers of it, and how can we handle anti-clone embryos and plant them and harvest them for useful salistutions and organs? How will we find an answer to that question? I struggled very deeply with this question when I was on the President's Council. That was the most fundamental question we were converged to address.

And I came up with what's a very unacceptable position in my own culture of university scientists. I decided that I was against embryo research. And I just want to add that although Rudy and I may have a difference of opinion on that, I really respect Rudy's position on it because I, in the President's Council, came up with an idea for how you might get embryonic-like stem cells but not create embryos.

And Rudy took the initiative here at MIT to do this project with mice and prove that it could be done. And if the induced polyprodence stem cells hadn't come up, that might be the way it was done today. I think there are ways to bypass the ethical controversies and wherever that's possible, I think we should do it that way in respect of human objections on this.

And that's a lot said in too short a time. Yeah, no, no problem. So what I would like to do is we're going to soon transition to audience questions.

I have one more question, but if you have questions from the audience, there are two mics located in the two aisles, so you guys can start lining up with the mics and we're going to start taking questions from the audience. But I have one more question while you guys are getting there. And the question is that I was recently reading the immortal life of Henrietta Lacks, so the book about the discovery and development of heila cells.

And one thing that kind of stood out to me, it's kind of an interesting parallel story. One of the development of these cells and therapies and scientific techniques that were spawned by this immortal cell line and then like the life of this family. And one of the things that stood out was that like along the way it talks about how ethics and medical research was continuing to evolve.

The things that were done when these cells were harvest would be unspeakable today, but that was common practice at that time. And so my question is that how can the scientific and medical community move to a place where it's not reactive, but proactive, I realize you guys are trying to do this. But it seems as if there's more people who are pushing the frontier, and it seems like usually what happens is we push the frontier too far and then the public says, "Whoa, that was too far, we need to put a law up." We put a barrier up after we've gone too far.

Is there a way to proactively put up something that will still promote progress? It seems as if the history has been, we go too far and then we regulate afterwards. To me, it's reasonably straightforward. You should do your research under the permissible rules, of course, animal, whatever, the rights that you have to follow.

Do your fundamental research and get your... ...by be very transparent. And then you have the obligation to tell the public or whoever wants to listen. If you apply this technology to no two humans, that is a possible consequence, right? Positive or negative? So people are informed.

So coming back to the... for me, the key border is really the application, the translation to medicine. And that's... so the basic research, I think, is free, more or less. But you have the obligation to inform.

Because if you don't do... if you think nobody would have done, let's say you post genetic research or to... to in manipulations, when should you have stopped that? When the DNA was discovered or when... the biotics were discovered because... ...there was a basis for this, right? So there's no way to stop basic research, I think. It's... it's a dead end road. So you have to get the knowledge with all the potential, to my opinion, with all the potential of misuse or right use and be aware of this and then make a decision.

Do you want to use it? Yeah, well, I... I'm very largely in agreement with that because I think basic research is the engine of... of transforming power. And as a physician, I know, for example, with CRISPR, they're... they're... probably way more now, but they're already 6,000... we'll soon have many thousands more, but we have already identified over 6,000 single gene diseases, 95% of which have no treatment whatsoever. That's... that's an amazing body of suffering in... in our civilization that we need to address.

I think one of the most important things about this current moment in... in this great story of the human drama of... ...emerging scientific knowledge and cooperative

civilization is... is... is... that we, at this particular moment, have a chance to think ahead, prospectively. And one of the challenges of this, and Jennifer Doudna and I, and I believe Rudy and all of us working together on this, I want to be very sure that... that the good that can come from this, the uncontroversial good does not get stopped because it excites too much opposition and in some cases reasonable opposition. And sometimes it's necessary to actually draw boundaries and say we won't do things just to keep the society coherent and to honor diversity of opinions.

And sometimes you need to have protective barriers. I... I don't generally favor legal moratoria. It's much better if you can do this by social consensus.

And yet there might be times when there need to be barriers. G. K. Chesterton has a... an interesting image where he says little boys are playing soccer on a field, but the field at the very borders of the field goes straight down to the... ...2000 feet to the cliffs and the rocks below where the ocean is pounding. And so where are they playing soccer just in the inner 30 yards? Maybe meters because it's Europe.

So, what was England? G. K. Chesterton. Meters. The arts.

They're in the... they're playing in the center of the field. But if you put a fence around the edge, safe, secure fence, they can play right to the borders. And so there's sometimes when you need to anticipate, draw boundaries, allow research clearly to some boundaries and not to others.

But in the final end, the... what governs a society is going to be... it's a large... you start out with worldview. Well, it's going to be large-scale questions of what the general ethos of the civilization is. And even in the matter of enhancement, I can think of some very good uses of enhancement.

So, for example, if I were a physician doing... if I were a surgeon doing surgery on a child's eye, and I could take a beta blocker, which is a kind of a... interferes with... with... ...well, I don't want to go into the biology of it. Basically, it'll steady the hand of the physician, the surgeon. If he's operating on an eye and it takes that for him to do a good job, even if it did something... ...you know, sort of in a minor way, not destructive to that person, I would think that's a reasonable thing to do.

Because in my mind, it's legitimate to give up something of your life for the good of something else. I think in some ways, I want to be used up in my life. I want every ounce of me to be used up in my life for the good.

And when I die, I'll be like having drawn down the entire bank account of my biological existence. But you see, the point is, for the surgeon doing the surgery, the goal is good. But how do you know the goal is good? Like, you started.

What's the good? Well, that's a large... that sets in the frame of a very large-scale

understanding of what life is for. And what gives meaning and what endows our life with dignity. And dignity is a hard word to define, but I think we all kind of know it.

We certainly know love when we see it. And if we operated with the large-scale principle of love, C.S. Lewis once said that we should answer all of our problems with more love, not less love. I think that's a very good guideline.

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