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INDEX

SESSION 5: THE GENOMIC "REVOLUTION" AND THE PRACTICE OF MEDICINE

DR. PELLEGRINO: Good morning. Our speaker this morning is Dr. Francis Collins. It's been customary, Dr. Collins, not to go into a long dissertation on people's accomplishments. In your particular case, that would be certainly overdoing it.

We don't have to say very much. No one is better known than Dr. Collins in this field. And so I just want to express our delight and our pleasure and our honor of having you with us. And you take off in the direction that you have indicated in your title.

Following Dr. Collins' presentation, the discussion will be open by two of the members of our Council: Dr. Janet Rowley and Dr. Bill Hurlbut.

Dr. Collins, the floor is yours.

DR. COLLINS: Well, thank you very much, Ed.

DR. COLLINS: It's a real pleasure to have a chance to address this distinguished group. And on this rather cold morning, nice to see you all here looking so bright and ready for an interesting discussion. That's what I'm expecting will happen here because I think the topic is certainly a timely one.

I know that in November at your meeting you heard presentations from Kathy Hudson and from Bob Nussbaum on this topic of where genomics is taking us as far as its implications for medicine. And I will try not to duplicate very much the materials that they went over, although there will be some unavoidable overlap of a sort. But I did have a chance to look at their presentations. So I think I know some of the ground that has already been covered.

So I thought what I would do is particularly this morning to focus on the science, to tell you about things that are happening. And they're happening quite quickly in the applications of genomics to understanding the hereditary factors and somatic factors that play a role in health and disease that are moving rather quickly in the direction of application in the practice of medicine, maybe not as quickly as some of us would like because we're impatient but certainly more quickly than I think a lot of practitioners are aware.

This is I think, therefore, an appropriate topic for this Council to consider because it also carries with it a lot of ethical, legal, and social issues, which I will try to mention a few of those anyway towards the end of the presentation. And then I hope we can have a vigorous discussion about all of this.

So we do, after all, have the circumstance now, a rather historic one, of having our own human sequence accurately determined and sitting in an internet-accessible database as a consequence of a Human Genome Project happening.

Interestingly, just about exactly 50 years after Watson and Crick's description of the structure of DNA, now in April of 2003, all of the goals of the Human Genome Project were completed, including this 3.1 billion base pair, human DNA sequence deposited all the way along by more than 2,000 investigators, who worked together to achieve this goal in a really remarkably efficient and selfless way.

But, of course, we are just beginning readers in a certain way when it comes to trying to understand that genome sequence, our ability to look at those A's, C's, G's, and T's and figure out what information is encoded there. And how it all works is moving forward, but we still have a lot to learn to try to understand how this script gets read and how sometimes glitches in the script result in disease risk.

I think many people, sort of excited as they were about the consequences of having our human genome sequence, now in 2007, 4 years later, are saying, "Where's the beef? Why haven't we completely transformed everything that we are doing in the medical arena?" And anybody working in the field would have told you that wasn't a realistic expectation, that this was a foundation. But now we have to build on it.

And I think this is a pretty good representation of the first law of technology, which is we tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run. And I think that will turn out to be true for genomics and we can decide what is the definition of short run and what is the definition of long run. But this law, which is played out in many other instances, I think will play out here as well.

So today I am going to talk to you mostly about things that are present now in the research arena, which I think will find their way into the clinical application, but some of them are already there. And clearly, as we try to anticipate the consequences of all of that, the time is now to pay attention and try to put into place appropriate considerations to be sure that this is all done in a benevolent way, that it helps people avoid or deal with disease, as opposed to putting them at unnecessary risks.

So many of us do have this future dream that medicine will, in fact, move into a phase where individual information can guide the process. You wouldn't think of buying shoes in a single size.

I'm quite sure that all of you here when you went to the shoe store did not just randomly pick a pair of shoes off any old shelf. You looked for the section that had your particular size. And then you applied other criteria to what you might want to pick out. But you certainly if you wear a size seven didn't start in the size ten section looking for what would fit you.

And, yet, for medicine, we have largely been forced to do that kind of generic approach because it was what we had. It was the best information we could go on.

We did some tweaking of that, you know, trying to adjust drug dosages by body mass index or body surface area and certainly treating children different than adults most of the time, although not always. But it has been still very much a one size fits all kind of approach in terms of the diagnosis, the prevention, and the treatment of disease.

And since we know we are all different individuals with different risks, this is not an ideal circumstance. And one of the promises of genomics is to try to do a better job of this kind of individualizing of the approach.

So let me just mention a few notes from the front lines here for using this metaphor of the genomic revolution, which, you know, is maybe not the greatest metaphor because it sounds all very war-like.

This is certainly not our intention here. But, in fact, it does seem as if there is a real groundswell of change underway. And so we may as well call it that. I guess that was the title I was assigned. So I'll stick to the word "revolution."

Let me just point out a few notes from the front lines of things that are happening, some of them just in the last year or two, that may not have necessarily reached the ears of the public to the degree that perhaps they should have because I thought this group of distinguished experts might want to consider what some of the consequences would be.

Some people somehow assumed that DNA sequencing was all over once we had gotten that reference sequence of a human genome and some other model organisms, like mouse and rat and dog and horse and so on, that that would sort of be it.

And that is obviously turning out to be a very narrow view. In fact, DNA sequencing is emerging as a tool for human medicine in ways that I think most people had not quite been prepared for. And the idea of being able to sequence any of our genomes for an affordable cost, maybe $1,000, could well be no more than 5 or 6 or 7 years away given the way in which the technology for doing this is moving forward so quickly.

Two instruments have found their way into our large-scale sequencing centers in the last year and in many other places as well. These machines are beginning to be tried out. And at a meeting in Marco Island, which is one of the gatherings every year where technology gets trotted out and discussed, the production efforts being built upon these instruments were truly impressive. And this is just two weeks ago.

So one of these is a machine called 454, which is a rather odd name, I suppose, for a company and an odd name for an instrument, but that's what it is. The idea of both of the two machines I'll tell you about is to get away from the traditional gel-based methods, which is basically the method that Fred Sanger invented back in the late 1970s.

All of the DNA sequencing we have done up until now has largely been to build better and better efficient steps into that gel-based dideoxy method of DNA sequencing. And it's served us very well. And we have driven the cost down by orders of magnitude, particularly because of the Genome Project and its need to do so.

But we are now seeing a real quantum change in the approach. And the two methods that are now finding their way into practice are really built on different principles. This one is done on beads, where the idea is that you attach DNA to specific beads. You amplify them on that bead.

And then — and here is the trick — you can then do sequencing at massively parallel platform arrangements so that, instead of in a typical current sequencing machine, where you might run 96 reactions at once, here you can run hundreds of thousands or even millions of reactions at once, simultaneously collecting all the data in a rapid way.

There are still bugs in these systems. Their quality of the data is not as good as the tried and true method that has been optimized now over more than 20 years, but it's coming along very quickly. And it's clear this is going to make a major impact on our ability to collect the DNA data.

Perhaps even more of an impact may come from this machine built by a company called Solexa, which again uses massively parallel approaches instead of beads. Basically the DNA fragments are attached to a surface and then amplified in place using a polymerase chain reaction so that you end up with clusters of molecules that can then be sequenced. And that's just, in fact, what one can do.

Once those clusters are there, you can actually see them affixed to the solid surface, as in this picture. And each one of those clusters can then be sequenced using an enzymatic reaction. These give you short reads but, as you can imagine, just a very high volume of them.

And it looks as if we have already reached the point of having the ability to sequence an individual human genome for something in the neighborhood of $100,000. And that is two orders of magnitude cheaper than it would have been if we had stayed on our current cost curve. And the expectation is that that will continue to drop.

Already individual human genomes are beginning to be sequenced by people using these instruments for research purposes. And you should anticipate that this will increasingly find its way into larger-scale research and ultimately into clinical practice of medicine.

And I think that is where the real growth area for DNA sequencing is: we're already now applying this kind of very high throughput in expensive sequencing to try to find the genes that are still out there unidentified from Mendelian disorders because there are many rare conditions where we have not been able yet to find the responsible gene. And to be able to sequence the entire genome or a segment where you know that the gene must reside, based on linkage evidence, is undoubtedly going to help a lot finishing out this work of identifying those conditions.

We know, for instance, there are probably 50 different types of x-linked mental retardation that have not yet had their genes identified. And you can imagine a project, in fact, that is now getting underway where you simply get DNA samples from large numbers of affected males and you sequence all of the exons of the genes on the x-chromosome.

And you can do that, actually, for a very affordable cost. And undoubtedly you will make a lot of discoveries of genes that are involved in brain function and that account for these particular conditions. And, of course, the hope would be that some of those will lead you in the direction of ideas about treatment.

Common diseases also sequencing can be now applied to candidate genes and as it gets cheaper and cheaper to just sequencing the whole thing. But perhaps a particularly attractive approach that is being undertaken right now with DNA sequencing is for cancer. This has been unaffordable until now, but now it is becoming so because this cost curve is coming down so rapidly.

The cancer genome atlas is a joint effort of the Genome Institute and the Cancer Institute currently being conducted as a pilot project on just three cancers, the three that you see here. And the goal is to sequence something in the neighborhood of two or three thousand genes in four or five hundred individual tumors of each of these types for which DNA is also available from blood so you can compare the DNA sequences and figure out what is a new mutation somatically and what is a hereditary change and not only to do sequencing but also systematically to look across the genome for changes in copy number, where you have delegations or amplifications, as well as to look at gene expression.

And we put all that data set together, together also, I should say, with epigenetic information. We may finally begin to have a comprehensive view of what goes on in these three tumor types. If this goes well, we would hope to expand this after the pilot phase to look at many more tumor types and apply the same approach.

Obviously the more rapidly the cost comes down, the more practical that is, especially as NIH is at the present time rather significantly strapped in terms of budgetary restrictions on what we can do.

And TCGA has several components. I won't dwell upon this. But basically it is a highly organized effort involving now dozens of laboratories that are working together to try to apply all of these new technologies to the same set of tumors and to put all of the data into a database where any qualified investigator can immediately see the results and there is technology development as well.

And ultimately, as I have been saying, I think the next step beyond these more focused efforts will be complete genome sequencing, initially for research and then as part of mainstream medical care. And that, of course, is some years away but not as many as one might think.

So what are we to do in the meantime for those common diseases like diabetes and asthma and schizophrenia, autism, hypertension, the common cancers, where we know there are hereditary factors? Some have been found, but a lot have not. Do we have to wait until we have the ability to do complete genome sequencing to find those variations or could we speed up the process now by taking some sort of shortcut? And, of course, I wouldn't answer the question if the answer wasn't yes.

So, in fact, there is a very exciting phase getting underway now about how to find those factors. If there are relatively common variations, we have the ability now to do that without having to look through the entire genome.

So here is the next sort of note from the front lines — the discovery of genes for common disease is happening, particularly in the last few months. And I think you're going to see in the next few months a virtually outpouring of discoveries about variations in the genome that are relatively common in the population that play a significant role in risks of common diseases.

The idea is to develop methods that can find the ticking time bombs that are residing there in the DNA. And we all have them, probably dozens of them. None of them carry a very high risk of going off. Perhaps if you have one of these, your risk might go up by 10 or 20 percent over the situation if you did not. And it's the combination of these particular genetic risk factors plus environmental exposures that generally is responsible for whether disease occurs or not.

And we need to uncover what both the environmental and the genetic risk factors are in order to figure out better ways to intervene. And, frankly, the genetic factors we're not going to be able to change, but if we understood how they occur, who is at high risk, and could modify the environment or the medical surveillance plan, that would be a good strategy for individualized prevention.

So how are we doing this? Well, basically what you would like to do would be to sample across the entire genome and find variations, here color-coded to make it somewhat simpler to explain the strategy, like variant b. So in variant b, our ten affected individuals have a higher proportion of the orange spelling than do the unaffected individuals, who have many fewer orange spelling individuals.

Most of the genome will not give you that kind of answer. If you're looking at a disease like diabetes, most of the genome you would not expect to see a difference between the cases and the controls. But somewhere out there if you accept the idea that some of the hereditary risk factors in common disease arise from common variants, you would expect if you had a systematic way of surveying the genome, to be able to find examples like this.

Now, my cartoon makes it look easier than it is because most of the risk factors you find are not going to have this kind of dramatic skewing between cases and controls. You're looking for a relatively modest difference because these are not going to be deterministic findings. They are going to be risk factors.

And so, instead of 10 cases and 10 controls, in general, you need 1,000 or more if you're going to have sufficient power to be able to assess the situation. And that has been the daunting factor.

That means you have to identify a large number of individuals with the disease and carefully characterize their phenotypes. And you have to have well-matched controls so that you don't end up chasing down false positive results that have nothing to do with the disease.

But the most daunting part of this until recently has been how would you actually survey the whole genome to do this kind of comparison? And so people have largely been forced to look at so-called candidate genes, which is to say you've got to have a hunch and you've got to go and figure out amongst the 20 or 22 thousand human genes what's on your short list that might be involved in the disease.

And the problem is for most diseases that you would like to apply this to, we're not smart enough to

know what the short list ought to look like. We're still pretty ignorant about the genetic factors in a disease like, say, diabetes.

And so most candidate gene studies have been pretty disappointing. There have been false positives that didn't hold up. There have been occasional success stories, but mostly it has been one long story of disappointment and frustration.

And, of course, you would like to get beyond that forced hunch, sixth sense situation, to be able to scan the whole genome systematically. And that's what we now can do, and that's why there is this real dramatic leap forward occurring in discovering these genetic factors because we finally have the tools to do this.

A big part of that comes out of this project which was an international project called the HapMap Project. I had the privilege of serving as the project manager of this effort, as I did for the Human Genome Project.

This was focused on that .1 percent of the genome where we differ, not the 99.9 percent where we're all the same. And we wanted to get a really good catalog of what that variation looks like in different parts of the world. And we were limited in how many different parts of the world we could look at.

So we basically looked in a population with northern European background. We looked at the Yorba tribe in Ibadan, Nigeria. And we looked at in individuals living in China and Japan. That was our sample. And it actually turns out that that's a pretty decent representation of the variation that you might have found in other places as well.

And what HapMap did was to basically tell you where the variation in the genome is and how it's organized into neighborhoods because it doesn't turn out that these variations in the genome are all independent of each other. They're actually traveling in a bit of lock-step, reflecting our relatively recent descent from common ancestors.

And the good news about that is that means that you don't have to sample all of the ten million variants that are common in the genome to find the ones that are associated with disease because they are associated with each other in local neighborhoods.

If you pick wisely, you can pick a much smaller set of these variants. And they basically stand in as surrogates for all the rest. And if you're smart about how you do the picking and that's what HapMap allows you to do, instead of having to look at ten million things, you may only have to look at a couple of hundred thousand.

That has now become possible with the kind of chips that are being used to do DNA genotyping. One can look at more than 1,000 cases and more than 1,000 controls with hundreds of thousands of these genetic variants and afford all of that for something in the neighborhood of one to two million dollars, which is a lot less than the cost of having collected all those cases and control in the first place.

And so there is a huge amount of interest and activity going on right now to apply those ideas to common disease. And the success stories are starting to build up.

The first success story and one of the most dramatic one is this common cause of blindness in the elderly, macular degeneration. Most people were not that convinced that this was going to be a disease where genetic factors were all that important. It doesn't come on until your 70s, 80s, or 90s. There was some familial clustering, but it wasn't all that impressive.

Applying the HapMap, Josephine Hoh and colleagues were able to identify a variant in Complement Factor H, which plays a very strong role in disease risk. And not too long after that, another major risk locus was identified, HTRA1. And just these two variations seem to account for about 50 percent of the risk of this disease. Another significant environmental risk factor is smoking.

So we have gone from knowing very little about the cause of this illness to having a much more refined picture and one that actually suggests the possibility of interventions because both of these genes seem to be involved in the inflammatory pathway. And it may very well be that prevention could then be mounted by using an approach that depends on anti-inflammatory agents, including ones that are already FDA-approved. So this is a pretty exciting story to go from essential ignorance about a disease to a really nice view of what is going on in the space of just a few months.

Other early results from HapMap from about a year ago, the identification of a gene, TCF7L2, in Type II diabetes, now confirmed by almost a dozen groups as a major player in risk of this particular

common adult-onset disease that causes so much mortality and morbidity; a variant associated with prostate cancer, which, interestingly, this variant is more frequent in African populations and might account for some of the health disparity in prostate cancer between different groups, although not all; and in *Science* a few months ago, an association identifying IL23R as a gene important in Crohn's disease. And this one also suggests immediately a therapeutic strategy that I'm sure is being pursued by more than one group at the present time.

And just three days ago — this is from online *Nature*, not yet out in print, another study of Type II diabetes, which both confirmed that TCF7L2 that we already knew about but also identified three other genes, including this guy, SLC30A8, which is a fascinating discovery and one which my own lab has already independently found, which is a zinc transporter that is only expressed in the islet cells of the pancreas. Insulin in the pancreatic islet cells is complexed with zinc.

And you can imagine how this kind of transporter, if it's not quite doing its job, might have an effect on the ability of your pancreas to make insulin when it's supposed to, also immediately suggests a dietary form of therapy, which might be a very nice nutrigenomics kind of outcome for this sort of discovery.

So these things are happening. And I tell you in the next two to three months I know of at least three or four other major papers that are coming out on other conditions, such as schizophrenia, that are going to be quite revealing in terms of finally nailing down some of the well-validated genetic factors that play out in diseases that have been so puzzling.

To try to stimulate this to go even faster, NIH has been engaged in an unprecedented public-private partnership, again trying to speed up this process at a time where NIH funds are somewhat constrained.

We built this public-private partnership using the foundation for NIH as the moderator of the whole thing and obtaining funds from the private sector to support what is basically a completely open access competition for individual investigators who already have collected samples from cases and controls of particular diseases to get access to this kind of high throughput genotyping.

The requirement is that all the data has to be put in a database, where any qualified investigator can see it. And that has been agreed to. And we had more than 30 applications for this particular competition. And when the dust all settled, these are the six studies that are now underway and already well into the pipeline.

Interestingly, four of those six are mental illness conditions. And we didn't necessarily expect that was going to be the case. It just reflects the fact that the National Institute of Mental Health was thinking about this five or six years ago and really preparing for the moment where this would become possible. And so they had already collected very well-characterized cases and controls, dealt with the consent issues in an effective way so that these samples could, in fact, be put into this pipeline and have the data from the genotyping accessible to lots of investigators around the world. And that's a serious issue for some of these studies where the consents are, in fact, going to be a problem.

So that's one big initiative that's underway. And then on top of that, just starting in the last couple of months and strongly supported by Secretary Leavitt, we have an NIH genes and environment initiative, which really is now trying to pull together advances in technology to detect environmental exposure in a more rigorous way than we have been able to do in the past. And by that I also include diet and physical activity.

There's a lot of opportunity here, particularly using cell phone technology, to do a better job of actually recording what people are exposed to, than the questionnaire-based methods, which have been the mainstay in the past. And this will also support additional genetic analysis.

And this is all being done in a coordinated, integrated way that David Schwartz, who directs NIEHS, and myself are co-leading. And this will involve the expenditure of $40 million a year for each of the next 4 years to try to speed up this process of identifying factors and coming up with strategies for intervention.

So I think it's fair to say we're going to see these major common variants for common diseases coming out — they already are — in the next two or three years, that we will go from a pretty significant level of ignorance to a much better informed situation about what factors are involved in disease pathogenesis.

And each one of those discoveries provides both an opportunity to suggest who is at risk by using this

diagnostically, but in the longer term, I think what we're most excited about is that this points you towards a pathway that could be used to target a therapeutic strategy.

We desperately need new ideas about therapeutics that go beyond our current hunches about what pathways are involved. And I think in the longest term, this whole business of discovering, using the tools of genomics, hereditary factors, and disease is going to have its biggest impact by revolution in therapeutics.

But we all know how long that takes because that means you have to come up with a hypothesis. You have to then go down the pathway of identifying a small molecule, of finding out whether it works in cell culture, then in animal models. Is it toxic? Does it have appropriate distribution, metabolism, and excretion patterns? And ultimately can you run a clinical trial, show benefit, and get it approved? So one should not expect the therapeutic impact of these discoveries that are happening right now in less than a decade or even more.

So let's move, then, to those clinical applications. Again, as I'm saying, I think the full consequences are going to take a while. But some of these things are coming along more quickly.

And they will all come sort of helter-skelter. It won't be every disease is moving through this pathway of gene discoveries and therapeutics at the same pace. A lot of that will depend upon how much energy is being put into it, how many resources, and also serendipity.

You know, you run into a gene, like that zinc transporter that immediately suggests a simple treatment. Well, you're much further along than if you encounter a gene than nobody has ever studied before and you have no clue what it does. First you have to figure out a lot of basic science about its function before you can begin to apply your ideas about treatment.

So let's consider, then, this flow of information that's coming out of this revolution in genomics. And I think what's basically happening now in a big way is the diseases with a genetic component, which is virtually all diseases if you look hard enough, are going to have their genetic defects identified because of these increasingly available and efficient tools.

Then the clinical implications will kick in. And probably first of all diagnostics because it is, at least in concept, rather simple once you have identified a variant that you are quite confident increases the risk of disease, then you could begin to offer that prospectively to people who might want to know.

And there are all kinds of interesting issues about why would people want to know. And a lot of that relates to whether there is, in fact, a preventive strategy associated with knowing you are at high risk.

After all, we have known for quite a long time, about 15 years now, that a major risk factor for Alzheimer's disease is having the e4 allele at the APOE locus. And, yet, that test is not very much used and is not all that interesting to most people because we have nothing to offer the people who are found to carry that allele other than to say, "Well, you might want to plan your future a little more carefully." And most people don't find that a sufficient reason to take the chance of getting information that could actually be quite distressing.

So I think perhaps what has been underestimated is just how important and how complicated it is to go from having a hypothetical diagnostic to being able to demonstrate that you do have an intervention that only sort of makes good common sense, but it actually works. You want to have that data, I think, before you begin to advocate for a change in the practice of medicine.

In some instances, we are there. Perhaps the best example in my mind is in cancer because familial cancer syndromes have as their mainstay early detection if you want to try to improve the outcome.

And certainly colon cancer is a wonderful example of this, families such as this. And this is a real family from Baltimore. Not too many years ago, if this person marked with the arrow here had come in asking what her risk is and whether there is something she should be doing about that risk, she would have gotten sort of a general recommendation that yes, you're probably at higher risk because of your family history. But there's not a whole lot more we can say than that.

That's all changed now with the discovery that families like this are extremely likely to have mutations in one of a couple of DNA mismatch repair genes, which can be tested for in this family. That was, in fact, done and showed that the affected individuals had a mutation in the MLH1 gene, which is a mismatch repair gene. And then that made it possible for the unaffected individuals who are at 50 percent risk.

And there are in this picture five of them to find out whether they also carry that mutation. And in this instance, that was done. And it turns out two of them do have that additional risk and are at about a 60 percent likelihood of developing colon cancer during their lifetime.

Now, here is a case where we have very good data to say that if you're in that situation, you should begin colonoscopy probably at age 30 or 35 and you should do that every year, not every 5 years. And with that kind of rigorously adhered to program, the likelihood of finding polyps while they're still small and easily removed before they become invasive cancers is extremely good.

And so here is a case where this kind of family history taking, which was an important start point — you notice here family history is not going to go out of date just because we have fancy ways of assessing DNA sequence. Family history taking followed by a thoughtful analysis of the potential here of a specific mutation being tested, followed by careful recommendations and implementation of those in medical surveillance is life saving and actually saves money as well.

Now, not all diagnostics are going to be on the germ line DNA. And, in fact, I think the area of greatest growth in diagnostics right now is actually in cancer and relates to somatic changes and particularly the effort to try to predict from what you find in a tumor, what's the likely future course for that individual.

And perhaps the most widely applied example of this is the oncotype DX approach, which genomic health has marketed for prediction about whether a particular breast cancer is likely to recur or whether it is very unlikely to and, therefore, whether adjuvant chemotherapy might be passed over.

And this is data from a paper now almost three years old showing that, in fact, the score, which is basically built upon an assessment of gene expression for a rather short list of about 17 genes, correlates reasonably well in a prospective way with the likelihood of distant metastases ten years later.

So this test, in fact, has been adopted by many oncologists in the practice of taking care of women with breast cancer, although the FDA is still questioning whether, in fact, this test is appropriate for them to intervene and try to regulate.

And, interestingly, FDA did approve a competing test just a couple of weeks ago based on a similar strategy but which requires frozen tissue, cannot be done on a paraffin-imbedded formalin-fixed section, which is where most breast tumors currently end up.

So it would be, in fact, unfortunate from the perspective of applicability of this test if only the frozen sections were useable. Many women would not be able to have the chance to learn about this. So that's an interesting debate that is going on in terms of how much FDA regulation and this kind of test is appropriate.

So that is the diagnostic part. A big area of current interest, which has grown rather quickly and which is I think coming closer every day to becoming standard of care but not quite there except in a few uncommon circumstances, is to apply this information about genetic variation to predict drug response.

And already now for almost two years on the market has been a chip that will determine an individual's variations in the p450 genes, which are responsible for metabolizing a very large number of drugs. And certainly knowing your genotype for p450 does have predictive value in terms of how you might respond to antidepressants and anticonvulsants and anticoagulants and a number of other drugs.

Interestingly, while this was marketed two years ago, the uptake has been very limited. And I think that's because most physicians are really not quite sure what to do with the information that comes out of this. There are really no good guidelines about how to take that information about somebody who is a poor metabolizer or an ultra rapid metabolizer and change the dose that you're prescribing of a particular drug. And I think that is an area where we need more data and certainly more education.

A drug where this particular approach together with other kinds of pharmacogenomic analyses might very well find its way into practice relatively soon is the drug warfarin or Coumadin, which is one of the most commonly prescribed drugs and the one which is used for anyone who has had atrial fibrillation with a risk of a stroke or a deep vein thrombosis. So this is an anticoagulant.

Many individuals, including my mother, are on this drug. It is a very difficult drug to manage. The window between an adequate dose and an overdose is extremely limited. And many people do, in

fact, suffer consequences, particularly at the initiation of therapy, because the drug dose turns out to be too high or too low.

And it's very clear in retrospective studies that you can make a pretty good prediction about what the maintenance and loading dose ought to be. If you know the individual's genotype at both p450 and at a gene called VKORC1, something like 55 percent of individual variation in the dose requirement comes from those 2 sets of genes. And we can now do that prospectively.

The question is, do we have enough data to begin to make that recommendation? Should the FDA now put this on the label, saying, "If you're going to prescribe Coumadin, then you should determine the genotype first?"

Well, there is an issue here. How do you get the data quickly enough? You've got somebody with a deep vein thrombosis. You need to start them on the drug. If it's going to take two weeks to get the genetic tests back, it's pretty irrelevant.

So we need to figure out how, in fact, logistically to actually implement this test. And most of us think if this is going to be the first one that we really try to move into practice and it will be a real sea change in the mindset of many practitioners, you want to be darn sure that this is actually going to help.

And so NHLBI and ourselves are organizing a prospective trial to compare the outcome using the genetic test versus using a dosing algorithm that incorporates everything else that we know is a variable, like age and gender, which are also important variables for predicting the dose. And we'll have to see.

And if, in fact, the genetic test adds only minimally to that and adds additional cost and logistical challenges, then it won't be appropriate to do this. If, on the other hand, you can show that including the genetic information reduces the risk of somebody getting way out of range or having a bleeding complication, well, then I think that will be a compelling case.

Maybe the first drug, though, that is ready for pharmacogenomics is not Coumadin, but it's a drug probably many of you haven't heard about, Abacavir, which is a very effective drug against HIV/AIDS. And, yet, about seven or eight percent of people who are given this drug get a rather severe hypersensitivity reaction, which can require hospitalization and can even be life-threatening.

We now know a lot about what that is about. And this particular hypersensitivity reaction comes about because of a variation in a gene in the HLA complex. If you happen to be one who carries the HLAB5701 allele, your likelihood of getting a hypersensitivity reaction to Abacavir is pretty high. And if you don't have that, it's essentially zero.

So this is a very attractive opportunity to try this out. And the Australians have done this, not just retrospectively but prospectively, and were able to show that when they introduced this prospective genetic screen, that they dropped the incidence of Abacavir hypersensitivity almost to zero. And this looks like, then, a good poster child for being able to implement a pharmacogenomic approach to a drug.

And we're talking intensely right now with FDA and NIAID about whether there is any need for additional data here or whether this is one where we already have enough information to take that step. And there are labs that will do this test and will do it in the space of 24 to 48 hours. And the need to prescribe this drug immediately, as opposed to waiting a couple of days, is not as compelling.

Ultimately, though, where you really want to get to in our diagram — and I mentioned this earlier — is the therapeutics. And that is going to be the longest lead time. And it's, therefore, going to be frustrating to us.

We have to, I think, take some comfort, however, in the fact that the strategy is a very appealing one. And in a few instances, it is beginning to play out quite nicely. And I can't come to this group and talk about therapeutic advances based on the genome without referring to the most compelling example, which comes out of the work of Janet Rowley but, of course, based upon work that was done a long time ago.

So one of the reasons this is now such a success story is that the basic work to get us here was started a long time ago. It wasn't a direct consequence of the Genome Project.

And this is, of course, Gleevec, a drug which turns out to block the active site of the kinase that is generated by this Philadelphia chromosome that Janet described, which is a fusion of chromosomes

9 and 22, seen in most patients with chronic myeloid leukemia. That particular kinase transforms well-behaved white cells into leukemic cells. And Gleevec, the drug that Brian Drucker and Novartis collaborated on, ends up blocking that active site.

Just recently, a couple of months ago, a five-year follow-up of this drug published in the *New England Journal* showing that, in fact, the long-term success here is really quite startlingly wonderful that there are individuals who become resistant to the drug. But, as you can see from this curve, all told here, the number of deaths related to CML after initiating therapy is actually quite small in a five-year period.

So we would love to see that replicated over and over again. I think that is the dream that we all have as we begin to discover these genetic factors involved in lots and lots of diseases, but recognize the pipeline is a long one to get to this kind of outcome.

I can't help but point out a couple of other examples where smart researchers aided by some serendipity may be able to short-circuit some of those very long steps.

This is the work of Hal Dietz at Hopkins working on Marfan syndrome. Hal was involved 15 years ago in the discovery of the gene, which is a gene called fibrillin. And everybody assumed this is a structural protein and that's why they have the heart disease and there's probably not much you can do about it because it's a structural protein.

Well, it turns out fibrillin has another function. It's also an inhibitor of TGF-beta. And it turns out if you have a mutation in fibrillin, you don't inhibit TGF-beta well enough and so you have over-activity of that particular factor. And that contributes substantially to the phenotype.

And in this paper, Hal was able to show that this drug, losartan, which is already FDA-approved for the treatment of hypertension, is also a TGF-beta antagonist and in this mouse model of Marfan syndrome essentially prevented the aortic dilatation, which is the cause of death in many patients with this disease.

And I've seen recent data that Hal has presented at meetings, showing that this drug, now given to children who have particularly a rapidly advancing course of Marfan syndrome, seems to stop the dilatation of their aorta as soon as the drug is started.

And there is now a big trial underway to apply this in a much larger group and compare it to the standard beta blocker approach. It looks very promising that, in fact, by banging away at trying to understand the biology of this disease based upon the gene discovery but not assuming that it is just as obvious as what it initially seemed, that Hal has happened into something here that might be an incredibly valuable discovery for the treatment of this disease.

My own lab works on this disease, progeria, the most rapidly progressive form of premature aging shown here in three pictures over the course of about 12 years of a young man with this disease, whose hands you see holding the photo.

We discovered the gene four years ago, found that it's a sporadic mutation in a single base pair of the Lamin-A gene that creates a dominant negative protein that results in the premature aging phenomenon.

But, again, because we fell into a pathway that other people had worked on for 20 or 30 years, Lamin-A has been the subject of much interest among cell biologists for a long time. And we know a lot about that protein. We are now about to initiate a clinical trial using farnesyl transferase inhibitors, which if I had more time I would explain the logic for.

Here is a girl with progeria on the treadmill getting ready for her to establish a baseline so that when the treatment is started, one can see whether it's working.

And, again, this is putting together a number of previous observations with gene discovery, with the fact that there are a lot of drugs out there that have been developed for other purposes that may potentially turn out to have unexpected uses.

And even cystic fibrosis, a disease that had certainly hoped to see advances now for quite a number of years given that the gene was published, the discovery was published, in 1989, we are now seeing because of this new approach of applying gene discovery to drug development drugs coming into clinical trials. And so the first gene-based drug has now entered clinical trials.

Just out of curiosity, this is the same person. This is Danny, who is on the cover of *Science*. This is a

couple of months ago, when I ran into Danny at a cystic fibrosis event. And he's obviously doing very well. But we need to come up with a better strategy as soon as possible for this disease.

This is an interesting cover. This is *Drug Discovery World*, one of these magazines that I don't generally read, but somebody gave it to me. And what are they saying the future of drug discovery is? GWAS. Well, what is that? Genome-Wide Association Studies.

This is HapMap-based approaches to understanding genetics of common disease, mapping the future of genetics. They're concluding it is going to be the best engine for therapeutic discovery that we have had in a long time. And I certainly agree. And it's kind of a cool cover, too.

So, finally, to bring this back more perhaps to this Bioethics Council in terms of the issues to worry about and to think about, certainly the attention to ethical, legal, and social issues, which have been part and parcel of the Human Genome Project from the very beginning, are more important than ever as we see this accelerating pace. And I'll just mention a few. And I'm sure others may come up in the discussion.

The number one issue for us at the Genome Institute from the very beginning from the 14 years I've been there, if you want to say what is the most important policy issue that we need to attend to, it's to prevent an outcome where people who find out information about their DNA have that used against them and particularly in health insurance and in the workplace.

Here we are, 2007. We still do not have effective federal legislation, but we are a lot closer than we have ever been. Going back a couple of Congresses, in the 108th Congress, a good bill that covered both health insurance and employment passed the Senate unanimously.

The House failed to act. So we had to go on to the 109th. In that case, the House did actually have a bill introduced, but, again, no action was taken upon it. And, as you know, the 109th Congress came to an end about two months ago. So now we're at the 110th.

And I'm happy to say that the momentum is certainly better than it's ever been. Both the Senate and the House have bills that were introduced early in the session. Both have now been marked up, the Senate bill a couple of weeks ago, the House bill just this week. And there is a growing enthusiasm for the idea that this might actually come to a vote on the floor of the Senate and the floor of the House.

I was very gratified when President Bush visited NIH a month ago and I had a chance to spend 45 minutes with him, he used a good chunk of his comments at the beginning of this session to talk about this issue of genetic discrimination and again to underline his perspective that this is a issue that needs a legislative solution and that he would hope to see this particular legislation passed.

And he would be prepared to sign it right away. So maybe we might actually get there this year. After many, many years of false starts and disappointments, I'm trying not to get excited because it is such a letdown when something falls through, but considering all of the tea leaves at the moment, this looks more promising than it has ever been.

The opposition here is largely coming from the Chamber of Commerce, who feel that, in fact, employers may be subjected to frivolous lawsuits if people who have been fired for good cause then come back and say, "Well, they did it because of my DNA."

And the bill is actually written rather carefully to try to discourage those kinds of frivolous lawsuits. And it's also I think important to note that more than 40 states now have legislation of this sort and there has not been a single such lawsuit in more than ten years.

Oversight. I know when Kathy Hudson came and talked to you in November, she spent a lot of her time focused on this and appropriately so. We want to find the right balance, but squashing an area of genetic testing between not squashing an area of genetic testing that is potentially growing rapidly and has a lot of promise but also doing something to put the brakes on tests that are actually not well-validated. And then it might actually do harm.

The FDA up until now has largely taken a hands-off approach. I mentioned that they have now started to look at these multiplex tests for breast cancer. Whether they also begin to look at other tests is an open question. And what other kind of oversight ought to be there, especially when you look at the wide, wide work of direct-to-consumer testing that is going on out there, some of which is really pretty bizarre.

U.S. News and World Report just a couple of months ago had a whole discussion about this, pointing

out in a pretty good story that these tests can show you risk, but how good are they? And many of them are not yet I think at the point where you would want to fully trust the results because most of the discoveries upon which such tests would be based are just now happening when you're talking about common disease.

I am actually concerned that this topic is still not getting as much attention as it should. It is easy to say, "Well, the 99.9 percent identity of human DNA ought to be an argument for saying how much alike we are and ought to be an argument for reducing bias and prejudice." And I think that has occasionally been an argument that has gotten attention.

But also as we look more carefully at DNA, it's clear that if you give me a sample of DNA and ask me, "Did this person's ancestors come from Japan, West Africa, or northern Europe?" I could answer your question given a few days in the laboratory because there are variations that are differentially distributed around the world, reflecting all kinds of migration patterns over the last 100,000 years.

It is even clear that there are regions of the genome that have been under recent selection. And you can see the signature of that. And for a very small number of those, we understand the reasons why.

So if you look at the beta globin gene, for instance, in the malaria belt, you will see evidence for selection. Well, okay. That's because that has been protective.

If you look at the lactase gene in people from northern Europe, you'll see evidence of recent selection that allows them to digest milk as adults; whereas, others in other parts of the world may not be able to do this.

But there are hundreds of these segments of the gene for which we do not know what the function is but clearly show differential selection depending on which part of the world you're looking at. And it would be hard to imagine that some of these aren't going to turn out to be controversial in certain ways. And it's not clear to me that we're fully ready to face up to that.

Again, I think the health disparity question is one of our most important issues as researchers, but it's a very complicated one. What really is the relationship between self-identified race and ethnicity? There are a lot of connections here. And people tend I think to blur through them rather quickly and maybe oversimplify.

Maybe in my limited view here, it's good to keep in mind that an awful lot of health disparities have nothing to do with genetics or heredity, but it related to differential environmental exposures, including education, access to health care, culture, socioeconomic status, and even things like stress. And those play a major role in health and disease.

But it's clear — and I mentioned the example of prostate cancer — that at least in some instances, there are genetic connections as well that reflect ancestral geographic origins. And those, in turn, are reflected in genome variation. And that, in turn, may then result in variance in specific genes that play a role in disease risk.

So self-identified race or ethnicity is a proxy for a lot of other information. The sooner we can get closer to the action and really identify what the proximate factors are that are involved in disease risk and stop using race or ethnicity as a surrogate, the better off we'll be, both in terms of the precision of our information and the lower likelihood that this is seen as a means of reidentifying the concept of race in a way that it doesn't deserve. We have got a lot of hard work to do, I think, to get through to that outcome.

Access is a big issue. As we contemplate the $1,000 genome, for instance, okay. Who is going to have access to that if it turns out to be valuable? It probably won't be everybody at once, at least not in this country.

I would refer you to what I think is a very thoughtful piece coming from the Secretary's Advisory Committee on Genetics Health in Society, a group which I'm sure this Council has been watching closely because they have struggled with many of the same issues that you all are dealing with in your discussions, particularly the ones about genetics.

And they, I think, pointed out all kinds of things that potentially could be done but require a lot of national will and political will to achieve because at the present time we're clearly not in a circumstance where coverage and reimbursement of tests and services based on genetics are on a trajectory to make access even and relatively straightforward.

When I spoke to this Council five years ago — and I looked back, it *was* five years ago — the topic was

enhancement. I think at that point the conclusion, and justifiably so, was that a lot of the scenarios that were being put forward about enhancement, like the *Gattaca* movie, which we watched a clip of that day, — right, Leon? — were rather fanciful. And we should spend our time worrying more about things that are realistic in the sort of ten-year time frame than things that won't happen during that interval, if at all. And I think probably that was a wise recommendation. And I wouldn't really stray away from it.

I think in terms of enhancement, the practical applications at the present time really fall much more in the direction of PGD, where you have an increasing ability to apply more and more kinds of genetic tests to pre-implantation genetic diagnosis. And the question is, where should those limits be set?

It's one thing to tests for Tay-sachs disease. It's another to test for gene variant for, say, obesity. And I know that there is a gene variant for obesity that will be published soon that is clearly highly validated. So is there going to be an application there that enterprising marketers to couples who determine to optimize everything will see as something they want to begin to offer?

And then there is this more philosophical question and one that I am very interested in and have been from the beginning. Are we running the risk with all of this excitement about genetics — and, believe me, I'm excited — that we overemphasize the role that DNA plays in humanity and undervalue other things, such as the environment, free will, and the human spirit?

And for me as somebody who very much enjoys the opportunity to seek the truth, not only scientifically but spiritually, I do worry that one of the contributors, one of many, to the increasing view of humans as more machine-like than spirit-like, may be our own field of genomics. And we really should work very hard to explain what this can tell us and what it cannot.

And in that regard, I seem to have had the opportunity recently to get engaged in conversations like this one in *Time* magazine, a debate with Richard Dawkins, who obviously is putting forward the view that what we're learning about genes and evolution means that we should sort of get over the idea that there is any need to consider things beyond that. My view is rather different. And this was an interesting experience, I can assure you.

So let me not go on any longer because I went on a little longer than I intended to. Basically I do think it is an appropriate and ethical stance to try to apply the tools of genetics and genomics to alleviate human suffering.

I think one of the least ethical things we could do would be to say we should slow this down. I would have a very hard time explaining that to the parents of a child who has an illness that desperately needs some new intervention.

At the same time, I think we would have to have our eyes wide open to the ways in which these kinds of advances may lead to misuses that society will be comfortable with. And that's why I'm glad all of you are spending as much time as you are in rooms like this thinking about those issues and trying to sound some sort of warning signals when there are things that need more attention than they are currently getting. And I am glad to be part of your process.

Thank you very much.

(Applause.)

DR. COLLINS: Shall I come and sit down over there? Would that be —

DR. PELLEGRINO: Yes, please. Thank you very much, Dr. Collins, for an absolutely superb, breathtaking, exciting review of the field of genetic medicine. You have really taken us from the molecule to the ethical and the social and even the spiritual. And it's been a great privilege to hear your presentation.

What we plan is to have two members of our Council open the discussion of your paper. And I will ask them to make their comments and then open the discussion to the members of the Council generally.

Our first discussant will be Dr. Janet Rowley.

DR. ROWLEY: Well, firstly, Francis, I want to thank you very much for your comments related to my own research in Gleevec and point out to members of the Council that Dr. Collins has been far too modest himself to point out that he has contributed to many of the things he described, including

helping to clone the gene for cystic fibrosis. So that he certainly merits the thanks of all of us and also I think the acclaim that he has received.

I can only echo Dr. Pellegrino in saying that, as always, Francis has presented a very dramatic and exciting talk. And it has been wide-ranging. So that when you think of a President's Council on Bioethics and think of the ethical issues that may be raised by the discoveries of the Genome Project, that, in fact, you covered pretty much what the ethical issues are and some of the status of trying to deal with those.

And I think that the question of trying to make sure that genetic information is not used against an individual or a family is certainly one of the major challenges that we face.

And I can remember when Clinton was president and I was president of the American Society for Human Genetics writing a letter on behalf of the society urging that individuals not be discriminated against.

And I think, unfortunately, many members, who are sort of similar to the pedigree that Francis illustrated of a family with colon cancer, in this case with the gene MLH1, but women will not get tested for VRCA1 because they don't want that information available to insurance companies or to employers, but I think in one sense women or families are more concerned about insurance and that this country has not protected those individuals yet, as I think a disgrace and an ethical, moral disgrace.

So that is an area I would guess with bills in Congress, that there isn't a whole lot that the Council can do except possibly to encourage the consideration and passage of that bill.

I think another issue that you raised, Francis, is that as a society and the physicians in that society are not really prepared to deal with considering diseases on this kind of genetic basis or probably more appropriate is how to evaluate information that is coming forward.

And, again, this is not an ethical issue. This is more one of education in saying that medical schools have got to do a better job of teaching medical students about the medicine of the future and about societies and other organizations to which physicians and nurses and other health professionals, the societies to which they belong have got to be important.

The question that I had thought of before we started was for you was going to be what the ethical issues were for the President's Council. And, yet, you have gone through most of them. I guess I would still come back to that question.

Are there issues that you didn't in your presentation have an opportunity to discuss as fully as you might have liked that the Council could deal with or are there additional issues that for constraints of time you didn't have an opportunity to speak about?

DR. PELLEGRINO: Thank you, Janet.

Dr. Hurlbut, you are the next commentator.

DR. HURLBUT: Actually, I would like to give as much time to Francis to answer the last question, but just let me make a couple of comments to frame this. It's obvious that we're talking here about a subject, right or wrong, that touches on the very meaning of origins and ultimate ends when humans think about their genetics.

And that clearly is at the foundation of individual and social identity and the grounding of morals itself. We tend to think of this in a very special way with regard to the causal circle of being, right or wrongly.

But it does strike me that there are some interesting things we ought to put into the mix of our discussion. You mentioned the issue of race and the parent exaggeration of determinism and so forth.

You [mentioned the 99.9% similarity between individuals]. I just want to point out that percentage has relatively little to do with biology in the sense that we have dynamic systems and we are percentage-wise very similar to chimpanzees, but there is quite a dramatic leap between us, at least in some characteristics. [So the basis of our moral equality must be something other than the percentage of our shared genetic sequence.]

Also, given the nature of gene-gene interactions and environmental interactions and so forth, most of our data on cause is going to be placed in terms of statistical probabilities. And there will even be

stochastic events that trigger certain dramatic changes in the outcomes of events, even if most things seem very similarly aligned.

So that strikes me as important. And, likewise, because of these confusing questions of determinism and the reductionistic model that genetics seems to promote in the common mind anyway, there is a special fear of genetics, both excitement and fear essentially, promise and peril, as it has been said 1,000 times.

And here is an issue I really appreciate some comment on, Francis. Apparently people are quite reluctant to go into studies that involve the use of their genetics. They're more willing to do studies that involve their RNA than their DNA.

And obviously if we're going to exploit the full possibilities of this field, we're going to use huge databases with demographic and epidemiological data. And you might comment on that a little bit.

I think, reflecting on what our Council might do, I think I would like some guidance because this is a subject that has been thought about a great deal, funded a great deal. And if you look at what has happened over the last 15 years of discussion, it actually hasn't moved that far in terms of conclusions.

So I would like your thoughts about what issues remain to be talked about deeply and what some avenues in to those might be. And, just to mention a couple that strike me, the issue of discrimination that you mentioned in the bill, some people have raised a question about whether that bill and our general social attitude sufficiently address the question of pre-implantation genetic diagnosed and whether families might be vulnerable to not having their children covered by insurance or so forth. Would you address that question for us, whether that's a subject that's been adequately dealt with?

Also, what I mentioned in the way of DNA records, recently there was an op ed. by Michael Crichton concerning patenting of genes. Would you mention something on that?

And, finally, two final things. One, could you say something about the advances in synthetic DNA synthesis and where that might lead us? And one thing that you only implicitly touched on that I would be interested in hearing about is you brought us back down to the notion of interventions that are preemptive or preventative medical interventions. If we could only know what was influencing disease development, we could perhaps go down to the bottom and prevent the expression of these diseases.

It does strike me that that presents a rather interesting dilemma for medicine. We don't want to intervene in a way that is damaging to an individual. A lot of disease expression is secondary physiological response to unfolding disease conditions. It might be much more subtle to intervene in these diseases than we think.

Do you get what I'm getting at there?

DR. COLLINS: No.

DR. HURLBUT: Not entirely. Well, quite a lot of disease symptomatology is actually the result of the body's response to a disorder. So, for example, tuberculosis is an immune reaction largely, the body's compensation mechanisms. And we could very easily target the wrong response.

Well, just go to the bottom of how we might intervene in genetic disease early in the special challenges in watching how we ramp up to that.

Do you understand what I'm saying? So those are the main things that strike me. And what I most of all would like to hear about is what you think we could do that others have not done.

DR. PELLEGRINO: Dr. Collins?

DR. COLLINS: Well, a very challenging pair of commentaries. And I'm not sure that I'm well-positioned to tell this distinguished Council exactly what direction to go in, but I will reflect a little bit on the number of issues that you all have raised. And thanks to both of you.

Maybe we'll go straight to this genetic discrimination question because both of you brought this up. Certainly there's no, I think, real disagreement from an ethical and moral perspective on this topic, that this is an issue of justice, that if, in fact, you don't get to pick your DNA — and we don't — that that should not be used to deny you access to health care or to a job that you would otherwise be qualified for.

The recent discussion about the details of the bill that you mentioned, Bill, in terms of whether, in fact, it's written appropriately to cover the circumstance of PGD has, in fact, represented the latest hiccup in trying to actually get this done.

I must say from my perspective, I think the bill is written in a way that covers those circumstances, but it quickly gets you into some pretty deep weeds as far as legal language of particular provisions.

And the fact that it has been raised — and you probably saw a letter from a Catholic bishop specifically pointing out the need to address this. And there was an amendment proposed in the House markup that would have changed the language in the existing bill, which did not, I think, pass — in fact, I know it didn't pass — and which actually worried a lot of the people in the Senate that the whole process might be falling apart on these grounds.

I would say this is an important issue, but I think those who are proposing changing the language of the bill to try to accommodate it really need to sit down very carefully and make sure that that is necessary because I think the coalition to get this bill passed still remains somewhat fragile. And there are lots of opposing forces out there that would love to see an issue raised that would slow down or stop the momentum.

This is the latest issue that has been raised. And I'm not sure that it is one that is understood well enough by those who are suggesting amendments to make those changes. And it could potentially derail the whole process. So I think we have to be very careful in making those kinds of proposals.

In terms of a related question, you asked about people's reluctance to participate in research that involves DNA testing, as opposed to RNA. We have done actually studies on that phenomenon by asking people who are otherwise qualified for NIH research projects and who decide not to participate, "Why was it you decided not to participate?" And it is this concern about discrimination.

And that's why they're worried about the DNA part. They get it that RNA expression is probably less likely to get them in trouble because it comes and it goes, but they understand that DNA is with you for life if you're talking about the germline part of it.

And once that information has been determined, you may not be able to pretend it wasn't. And it could in the current circumstance come back to haunt you, especially if you have to apply for an individual health insurance policy down the road, which is the part that is currently not protected.

Fully one-third of people who were in a situation similar to that family I showed you with colon cancer, who were given the chance to participate in a research study at NIH to go through the process of genetic testing and counseling and particularly to monitor what do they do with that information, do people actually change their health behaviors, do they enroll in colonoscopy programs, do they follow them rigorously, we need to know all the steps here.

A third of the people who were in the same high-risk situation as the woman I showed you in that pedigree ultimately decided not to participate because of this concern about discrimination.

So this is a very real and present issue. And the legislative solution, it seems to me, would have a huge impact on that. Whether it would reduce that risk completely to zero or whether people would still have anxieties about what might happen in other areas, like long-term disability or life insurance, which are not currently covered, I don't know.

By the way, those are topics which we have essentially avoided getting into in this country. And that might be an area that is worth some consideration. I think people have been anxious not to distract the conversation from the highest priority of discriminatory circumstances, which is health insurance and the workplace, by raising these other issues, but they are going to be there.

In the U.K., there has been a pretty productive discussion about life insurance, for instance, with the conclusion being that also there needs to be some ability for individuals to be able to at least get a basic level of life insurance, which you need in many instances to get a home mortgage, without having questions asked about your DNA. In this country, we really haven't had that conversation.

Long-term disability will be a very difficult one because I think you can argue there that adverse selection could come into play and that if you know you're at high risk for Alzheimer's disease but the company issuing the disability policy doesn't know that, you're really going to destabilize the economics of long-term disability insurance. And that will be an interesting and difficult area to get into. And, as I say, presently we really haven't had much progress in that direction.

So, again, I guess maybe because it is the big elephant in every room that talks about ethical, legal,

and social issues coming out of the Genome Project, genetic discrimination comes immediately to my mind in a response to both of your questions but other areas.

You mentioned intellectual property in the sense of asking about Michael Crichton's op ed. I don't know how many of you read Crichton's book called *Next*. Well, I have.

(Laughter.)

DR. COLLINS: It's rather fanciful. It includes a cloning experiment gone awry that results in a sort of chimeric chimpanzee human. It includes a parrot who seems to have remarkable abilities to speak and think. And they all get mixed together in this sort of "biotechnology gone wild" soup and a great deal of additional sort of political commentary as folded in there by Crichton about how intellectual property is really the evil that has resulted in all of this. And biotechnology doesn't look good in Michael Crichton's book, as you might imagine.

In the appendix, he sort of goes on a bit of a tear about what he has learned about this and what should be done. I think there are a number of aspects that he has got right and a number of aspects that I don't think are quite properly presented in terms of the facts of the matter in that op ed.

I am certainly one who has for the last 14 years, since I have been at NIH, tried in every way to discourage the idea of patenting information that in the past would have been considered foundational and pre-competitive and ought to be in the public domain.

You have seen NIH move successively in the direction of not only saying that but enforcing that by issuing guidances about intellectual property claims in genomics and by putting as conditions of grant awards those kinds of statements that "If you're going to do this, your data has to go into the public domain immediately."

I think we have had a pretty positive impact there. And I think the landscape really has changed. Crichton's complaints in the op ed. would have resounded more ten years ago than they do now.

But we do have this legacy of a big mess that got created during the 1990s, when there was, frankly, a bit of a gold rush going on by people claiming intellectual property on snippets of DNA sequence whose function was really not known and getting in some instances the Patent Office to issue very broad coverage of those claims in a way that now ties things a bit in knots for people who are trying to do follow-on experiments that might actually help the public. So I think the big problem we really have to deal with is more what, the mistakes we made in the past than quite so much the present.

We are still pushing that envelope as hard as we can, not just for DNA sequences. We have a new program at NIH to make it possible for academic investigators to get access to this high throughput screening process to find small organic compounds that have activity in interesting biological essays and that might ultimately lead to the development of a therapeutic.

And we have insisted that all of the participants in that project put all of their screening results up on the database called *PubChem* immediately without claiming intellectual property.

There was a big squawk about that, particularly from universities, who I think kind of overvalued what it is that you get out of a very early stage screen of this sort and thought that they ought to be able to hang on to this information and patent it and maybe not publish it for a while.

I, frankly, think that is not the way you are going to lead to the kind of public benefit that the program was set up to do. So we have held the line on that and insisted that if you are part of that program, all the data has got to go into PubChem and no IP can be filed. I think people are now getting used to it. Every time you come into a new domain here, there is one of those issues.

With all of these genetic association studies that NIH is funding, there is a discussion going on right now and lots of public input has been sought about whether, in fact, the discoveries that come out of that ought to be placed in the public domain or whether if you have found a variation in a gene like that zinc transporter I told you about that's associated with diabetes, that you ought to be able to patent that as a therapeutic.

Our arguments are that the patenting really ought to apply to further downstream efforts once you actually have shown something that's on the pathway towards public benefit. And so our insistence is that all that data also goes into a public database immediately. And, therefore, patents cannot be applied to it.

We are encountering some resistance on that point, but I do think just looking at the landscape over

the last 15 years this pendulum has really swung from where it was in a real land grab environment to a much more sanguine realization that if our goal here is to advance science and to benefit the public, you don't want to put a lot of toll booths in the way early in this road towards discovery. You want to let people travel on it freely and quickly.

You asked about DNA synthesis and the ethical issues there. And I am glad you brought that up. I didn't have time to mention it, the abilities to basically make any DNA sequence at will. While they are not moving forward orders of magnitudes every year, they are certainly improving substantially.

For instance, in a program we had been leading for the last four or five years to try to get all of the human full-length coding regions of the genes into a public database that everybody could have access to and other means of sort of spurring research, we realized about a year ago that, instead of trying to identify those coding sequences from some library, that it's cheaper now to just make them.

And so we are now synthesizing those genes from, you know, organic chemicals at a more affordable cost. And that tells you we really crossed a line somewhere. And I don't think it's out of the range of possibilities that many laboratories in five or six years won't bother to store all of these clones that we keep around and fill up our freezers with stuff we can't even quite remember what it was. You'll just, instead, make it and say, "Oh, well, I need that vector with that sequence with that particular mutation," punch it in the computer. Tomorrow morning there it will be because the synthesis will be just that good.

But, of course, that raises the specter of how this might play out if falling into the wrong hands and people begin to make pathogens that are really horrible.

And I think the group at NIH that is considering all of the consequences that may come out of advances in biotechnology that could be used for bioterrorist purposes are quite concerned about this issue of DNA synthesis and is there any way to try to keep track of that.

So that, for instance, companies that are providing that service monitor what it is that people are asking them to make. Instead of just saying, "Oh, it's just all A, C, G, and T. It doesn't matter," we need to have some kind of system of keeping track of that.

That will work for a while as long as most of the synthesis can only be done in a large facility, but it won't work forever if it becomes increasingly portable. And that's an area to keep track of.

I need to quickly sort of get to the meat of your question, Janet and Bill, what other issues and where do you think that the focus might be for this Council.

I have to say I come back again to this concern about genetics and the study of genetics and how that impacts our concepts of race and ethnicity and what it means to be human.

All men and women are created equal, endowed by their creator with certain inalienable rights. How is that affected by our increasing ability to discover that where your particular ancestors came from is going to be reflected by certain things that have been selected for in your genome that might not be there were it not for that history?

Those hundreds of places in the genome that show those fingerprints or those footprints of that kind of selection are ultimately going to bit by bit get figured out.

And some of them will be simply understood and noncontroversial, like your ability to drink milk as an adult, but others of them will be more controversial in terms of your abilities in certain intellectual ways. It's possible. It's going to play out there.

Behavior traits. We don't know what is going on there, what kind of influences down through the last 100,000 years have shaped the genome in different ways depending on where you are.

As we apply the tools of HapMap and the ability to scan across the genome to find subtle variations that play a role in disease risk, people are also applying those to look for things that aren't diseases.

Intelligence is clearly going to in the next couple of years have variations discovered that are associated with how you perform on an IQ test. That's inevitable.

Similarly, behavioral traits that you measure on a personality test, some of which have already been discovered, although some of them haven't held up very well, we're going to have a big outpouring of that as well. And if those are differentially distributed across different geographic groups, people are going to draw conclusions about that.

And people will use that for demagogic political purposes in certain ways that we will all find offensive. But are we prepared to come up with an appropriate counter response or are we kind of headed into a future and a not terribly distant future where the wonderful idea that genetics is going to bring us all together will, instead, be used to drive us apart? I am deeply concerned about that.

And I don't think at the present time we have a particularly well-coordinated strategy. It's one of the things when I meet with my staff that works on ethical, legal, and social issues that's always at the top of the agenda.

There are many perspectives about this that are I think not fully cognizant of what is happening in the field of genetics yet because it's come along so quickly. We need to have a strategy here. And it needs to be a strategy that reflects our shared principles of equity and justice. And I think there's a lot of work to be done there.

DR. PELLEGRINO: Thank you very much, Dr. Collins.

I would like to now throw the discussion open to the Council members. We are close in time. So I will take the Chairman's privilege of extending this discussion to 10:15, rather than 10:00 o'clock. So if you indicate your desire to speak, I will recognize you in some sort of order. Dr. George and Dr. Meilaender in that order.

PROF. GEORGE: Thank you, Dr. Pellegrino. And thank you, Dr. Collins, for that wonderful presentation.

I would like to explore with you for a few minutes those philosophical questions that you touched on at the end and then again at the end of your responses to Janet and Bill.

As a way in, I would like to just quote to you from a paper that was included in our materials, though not for this session, for our next session, in which an eminent philosopher, Daniel Dennett, says the following, "Science has vanished the soul as firmly as it has vanished mermaids, unicorns, and perpetual motion machines. There are no such things. There is no more scientific justification for believing in an immaterial and immortal soul than there is for believing that each of your kidneys has a tap dancing poltergeist living in it." Is that so?

(Laughter.)

DR. COLLINS: That's quite an interesting way to phrase the question. So I know Dan Dennett.

DR. PELLEGRINO: Yes or no?

DR. COLLINS: He and I have occasionally debated this issue about science and faith. And, of course, his book *Breaking the Spell* got a lot of attention about a year ago when it came out and expressed many of the same perspectives that are included in that quote, which is really quite a zinger.

I think the problem with what he is saying there is that it basically applies a scientific approach to a nonscientific issue. And so it's guaranteed to get you nowhere.

If there is such a thing as a soul, science is not going to discover it. If there is such a thing as God who is outside of nature, science is the wrong way to discover him or her as well.

And so in the same way that I think this argument coming from the sort of extreme atheistic wing of the scientific community doesn't get you very far, it basically takes the tools of science and applies them in a place where they don't work.

So obviously science is the way, the tried and true, the dependable way to find out the truth about nature and how it works. And one should not settle for anything less than scientific proof if you're trying to ask a how question about how something in nature actually operates.

But if you're trying to ask questions like "Why are we all here or is there a soul or is there a God? And if so, does God care about me?" it's immediately apparent, I think, as soon as you step back for just a minute from that question to say, "Science is the wrong way to try to approach that answer."

From my perspective — and I wrote much more extensively about this in this book called The *Language of God* that came out last summer — it is truly unfortunate that we have arrived at this point in our culture, where there seems to be a battle going on between the extreme views, where we have atheists, some of them from my scientific community, arguing that we ought to just get over this idea of faith, that it's a throwback to the past.

On the other hand, we have people of strong fundamental faith who say that science can't be trusted because it contradicts certain views that they hold about the origins of the Earth and human life.

Most of us live in the middle. Most of us are pretty happy there. Forty percent of scientists are believers in a personal God. It really is unfortunate that there is so much noise coming from the extreme perspectives that people are beginning to wonder if that is all there is.

I find that particularly difficult for young people, particularly young scientists, who are being told that you have to make a choice between these world views. That choice is both unnecessary and unfortunate.

PROF. GEORGE: If 40 percent are believers, that would suggest that 60 percent are either nonbelievers or agnostic on the question. Would it be fair to infer from that or perhaps just from other information that you have available that a substantial percentage of scientists, perhaps not a majority, agree that science has vanished the soul?

DR. COLLINS: I think that is a very strong statement. And I don't think most scientists would probably acknowledge the truth of that statement. A few would.

I think most of that 60 percent, although the data is not particularly strong here, are not scientists who are in the strict atheist community in the way that Dan Dennett and Richard Dawkins and Sam Harris are. I think they are mostly people who are agnostic who basically say there is no way to know. They are not particularly hostile to religion, but they are just not themselves participants in that world view.

Frankly, I think many of them haven't given it much thought. And I say this because I used to be one of those.

PROF. GEORGE: So you would say that most scientists don't believe science establishes what these philosophers claim science — that these scientists have, in fact, shown?

DR. COLLINS: I think in the phrasing that Dennett puts in there about science having disproved the soul, most scientists would have trouble agreeing with that.

PROF. GEORGE: My way of framing it would be that science is concerned with understanding material and efficient causes if I can use those old categories. And then the effort to suppose that since science is concerned with studying efficient and material causes, there can't be any other cause. In other words, there can't be formal and final causes.

DR. COLLINS: Sure. If you imagine a circle that contains all the truth that could possibly exist now or forever and then you ask what is the scientific part of that circle, it's not the whole thing. And so if an answer to a question you're looking for happens to be outside the scientific circle, that doesn't mean it's an inappropriate question. It just means you need another way to approach it.

PROF. GEORGE: Now, the question that you raised at the very end of the response to Janet and Bill about how they relate to each other, does that mean that the answer to the important question about how we will, whether we should, sustain the belief in the fundamental equality and dignity of human beings is something, a challenge that has to be met, not with the resources of science itself since efficient and material causes are not going to even in a deep understanding at the moment explain the basis of human equality and dignity, that science itself will have to be subject to judgments brought from beyond science, where we can explore realms of knowledge that would enable us to judge, in fact, that all human beings are created equal, endowed by their creator with unalienable rights.

DR. COLLINS: I certainly would agree with that. In my view, morality is not sufficiently explainable by scientific or even evolutionary arguments. Otherwise you're forced into the conclusion that right and wrong are simply an evolutionary contrivance and artifactual sort of representation of something that has no absolute truth associated with it.

And when it comes to the principles of justice and equity, I think those are principles where science needs to be brought into the conversation so that we know what the facts of the matter are about how humans are similar or how they're different, but I don't think we're going to resolve the issue about equality and justice based upon purely scientific arguments.

DR. PELLEGRINO: Thank you. We have four members of the Council who wish to speak. The time is short. And I would like to please ask that you be as direct as possible out of deference to your colleagues, who would like to also participate. Dr. Meilaender?

PROF. MEILAENDER: This is very brief, actually, but you puzzled me near the end, when you were talking through the various ethical questions that you saw arising. And you came to enhancement. And you recalled being here five years ago and you said when you were here five years ago and talked about it, sort of general agreement that certain things which were interesting to think about were not really likely to happen in the near future.

And the way that sentence was moving, it sounded as if what it was about to say was "But it's a little different now. It looks a little different now than it did five years ago, but it sort of just petered out at that point and didn't conclude anything."

Do you hold the same view? Do you hold a different view? What is your view on that question?

DR. COLLINS: Well, Janet will remember this because we certainly tried to struggle in that discussion about differentiating between the designer baby scenarios that make good Hollywood movies but really don't have much scientific legitimacy to them and to things that might actually happen.

I think some of the things we talked about that might happen in a ten-year horizon, things such as using human artificial chromosomes, for instance, to introduce a new set of genes that weren't already there haven't actually moved very quickly over the course of those five years.

The one thing — and I was at that point aware that I was running out of time. So I probably did hurdle forward rather quickly at this point in the presentation.

The one thing that we did identify, which I do think has moved forward, will continue to move forward, and is deserving of a lot of attention, is the use of pre-implantation genetic diagnosis, not that you're going to use that as a circumstance to insert a new gene, not that kind of gene intervention, not that kind of enhancement, but that you're going to try to skew the odds basically by having a number of embryos and picking the ones that you're going to re-implant based upon a DNA test that you perform, a biopsy, if you will, on those embryos.

And, again, there is increasing availability of that technology over the last five years. And there is certainly increasing knowledge about genetic factors in conditions that are increasingly more like traits than there was five years ago.

And I mentioned obesity in my remarks as an example that might be seen as appealing to some enterprising provider of IVF services. I don't know whether that will happen, but that is the sort of scenario I think to think about, which five years ago we could think about, but now it's getting a little closer to reality.

So I guess if I had to focus on an area of enhancement that deserves another look, that would be it.

DR. PELLEGRINO: Dr. Kass?

DR. KASS: Thank you.

I could listen to you all day. Thank you for this presentation and for your absolutely spectacular leadership, not just in terms of science but in bringing this conversation to the public. You've done it here. You've done it everywhere. And everybody should acknowledge with gratitude your service.

I want to leave these large philosophical questions alone. I want to come to the practical questions of the translation of this genomic knowledge into clinical medicine.

In the paper that you submitted, there is a nice paragraph which says, "Health professionals will need to become genomically literate. New curricula of educational models must be developed. Behavioral science research will need to establish how best to use genomic information to affect health behaviors and outcomes," all that sort of stuff.

There's a lot packed in there. And there's a certain irony to me in the little slide which was shown twice, "Personalized Medicine: A Future Dream." I mean, there are some of us who would say leaving genomics out of it, personal medicine of the sort you and I were trained to practice seems to be a vanishing species.

I guess there are two issues. One is given the doctor-patient relationship and its dwindling character, given the amount of education that would actually be required to discuss risk management when you're dealing with statistical evidence here, statistical factors at best, doesn't that particular part of this — it's not just a matter of information. It's a matter of the institutions that could act on that

knowledge and do the kind of education with stuff which is really not intuitive for the average patient. That would be one.

And yesterday we had long discussions, several discussions, about the efficacy of preventive medicine, which involves people's changing behavior for things for which we have 100 percent correlations, not 100 but very, very high correlations, of behavior and misery. And Dan Foster took the very dour view that we just can't do very much about making people change, even when the evidence is staring them in the face.

So, I mean, the slides are marvelous. Some of the innovations are marvelous when it comes to these targeted things. But in terms of risk management, the first side, shouldn't we be much more modest about our ability to use this knowledge efficaciously until we have either a different way of doctors relating to patients and the other matter about actually affecting people's behavior based upon this knowledge, which is, at best, merely statistical and from the patient's point of view like astrology?

DR. COLLINS: Those are great questions, Leon, as usual. I think you have cut very much to the heart of the question about the applicability of all of these discoveries, when it comes particularly to the prevention arena.

You could argue that the therapeutic arena is more likely in the long run to have a bigger impact because basically what you're talking about there is a discovery engine for new approaches to developing therapies. As long as we at least have a medical care system that's capable of diagnosing and treating, having treatments that work better would be a good thing and would probably advance things.

How realistic is this individualized prevention strategy going to be? There are a lot of roadblocks. And you have mentioned most of them. Certainly this circumstance, where at the very time you would hope physicians would have the opportunity to learn about this and to spend the time necessary interacting with the patient to walk through this complicated information is the very time where they're being taken increasingly to task for spending more than four minutes per patient. It doesn't look like a very promising scenario.

Actually, ten years ago we founded with the AMA and the American Nurses Association an organization called the National Coalition for Health Professional Education in Genetics, NCHPEG, which now has more than 100 member societies.

And it's increasingly clear to me it's not the physicians that are probably going to carry the load of this. If we do see this kind of genetic information finding its way into a discussion with an individual about their own prevention strategies, it's probably going to be someone like a nurse or a nurse practitioner or a physician assistant who is able in our current cost system to spend a little bit more time.

And we will also have to use heavily teaching aids that are based upon computer learning approaches, as opposed to having everything done in a one-on-one fashion by a busy and expensive health care professional.

Let me also address, though, your question about will people actually use the information or it will just be like "Okay. That was nice. Let me go back to doing exactly what I was doing." We don't have good data on that.

A lot of the intervention about health care behaviors is pretty discouraging when presented with information that ought to be motivating. People don't always get motivated.

Now, a lot of that comes out of cigarettes. And we have to acknowledge there is an addiction issue there, which makes that a lot more complicated potentially than some of the things that we will be able to offer up that come out of genetics. But one shouldn't minimize the fact that we really don't have a lot of data.

We just started a project at NIH where we're going to offer people, hundreds of them, the chance to come and be tested for all of the things that we know currently are validated as predicting future risk of illness.

We'll let them decide whether they want all of the information or just the ones where an intervention is available. We will then give them the kind of counseling about what kind of change in health care behavior or medical surveillance would be appropriate for their circumstance. And we'll watch and see what happens.

We need data because right now it's really hard to know what the answer is going to be. You can look at a little bit of encouragement perhaps from our cholesterol experience. I mean, the idea that we should all sort of know what our cholesterol is and if it's too high, we should do something, that has found its way into many people's attitude towards their medical management.

And the evidence is pretty good it's actually doing some substantial good in terms of the long run. Not everybody will agree with that I would judge by your raised eyebrows, but it does seem —

DR. KASS: Dan thinks it's statins.

DR. COLLINS: Right. Well, why do we have so many people taking statin? Some of them because they have their cholesterol measured and so they figured that they needed to do this. So if we had a statin equivalent for a lot of the genetic risks that are coming out of current discoveries, you can imagine an improved outcome.

But you are so right to point out all of the uncertainties here. And I didn't mean by putting this diagram forward to say that we're confident exactly what the consequences will be.

The pharmacogenomics part maybe is going to be a more clear success story, but we don't even know that yet. The therapeutics I'm sure will be, but it's a long lead time.

The individualized preventive medicine strategy, where we alter our health behaviors based on genetic information, it will be interesting to see what happens.

There will certainly be people who are sort of information seekers who embrace this and run with it, but is that going to be one percent or is that going to be 50 percent of the people who have the chance to get the information? I don't know. I just wanted them to have a chance to get the information without being fearful of it.

DR. PELLEGRINO: Dr. Dresser?

PROF. DRESSER: Thank you.

I have a general question and a specific question. The general one is you haven't said anything about proteomics. And after the Genome Project was done, everyone said that is the next big thing.

So are there any ethical implications, developments we should know about? And the specific question is — I'll try to get it right — a critique of the anti-discrimination approach to health insurance and genetics, genetic exceptionalism Mark Rothstein has raised.

So if it's unfair to use underwriting, to use a genetic predisposition in insurance understanding, then why is it fair to use an actual genetic disease, like breast cancer related to the bracketing in underwriting as a preexisting condition?

And if that's unfair, why is it unfair to use another kind of breast, somebody who has another kind of breast cancer that we haven't found the gene that it's related to, to exclude them in underwriting? And if that's unfair, why is it unfair to exclude someone who was injured in a car accident?

That is, if you consider the unfairness in this narrow genetic predisposition area, that's a drop in the bucket and doesn't address the larger unfairnesses in individual underwriting.

DR. COLLINS: Another set of good questions. Proteomics quickly I think is moving forward. I was one of those who was considering that the buzz about proteomics might be a little premature. It's very difficult to do this. You have to deal with five or six or seven orders of magnitude in abundance if you really want to sample all the proteins in a particular body fluid or in a cell.

And we don't have the technologies yet to do that reliably and effectively and reproducibly. So a lot of this has just been technology development. We're not there yet.

There have been some advances in terms of the ability to look at proteins that are in circulating plasma or serum and make a guess about what's going on internally in the rest of the body, but those have been hard won and not always well validated. So I think the promise of proteomics mostly still lies ahead.

In terms of the discriminatory or ethical issues, I think the fact that proteins are, after all, synthesized as a result of instructions provided in DNA. That means the connection is pretty tight. And most of the same issues apply. But certainly if you're talking about individual variations that pose a risk of future illness, yes, it's the same kind of story.

Now, in terms of exceptionalism, — and I know this has been an area of considerable discussion and rightfully so — it is probably the case that the fact that there is so much public concern about the use of predictive genetic information in health insurance is in a certain way an indictment of our whole health care plan and the fact that we in this country have more than 40 million people who don't have health insurance and that we are able to somehow live with that and not find that already to be a violation of certain principles of justice. It does, I think, point you to the — the fundamental problem may be much deeper than whether or not genetics is covered or not covered.

But genetics does in the public mind and with a certain legitimacy occupy a special place. It does, after all, carry predictive information. It is permanent. It is not like a blood test that's here today and gone tomorrow. Once it's there, it's there.

It is family-relevant. So the test you have has implications for your relatives, and other tests don't carry that. And it's personal. People feel somehow that this is private information in a fundamental way that may not apply to other kinds of laboratory tests that are conducted upon them.

So I do think there is a legitimacy towards carving this out, but in a certain way maybe it is also a way of saying we have a fundamental problem. We're going to try to fix this one now, but let's pay attention to the fact that this is not the only problem that we have.

Again, your examples about why genetic information should be given a special place here and not used in a discriminatory way; whereas, others can, again, it's not being argued that if you have the diagnosis of a disease that happens to be a genetic disease, that you no longer can be subject to underwriting.

It's the predictive information in a currently undiagnosed healthy person that is off the table. So that's different than the person who already has cancer or the person who already has a broken ankle. It's this predictive stuff.

So you might say then, "Well, you shouldn't be able to use your cholesterol either for underwriting in a health insurance plan." And there is some argument about how much of cholesterol is genetic anyway and where the boundary is there.

But I think the line that is trying to be drawn is saying genetics is special for the reasons I outlined and we're just talking about the predictive part. And it is a serious problem now in research, and it will be soon in terms of clinical practice.

DR. PELLEGRINO: Professor Gómez-Lobo and Dr. Hurlbut? And then I'm afraid that will have to be the last question since we'll be extending the period until 10:30.

DR. GÓMEZ-LOBO: Just a brief information question. Could you explain to us the contents of that amendment in the bill that has been submitted to Congress with regard to the discrimination issue?

DR. COLLINS: I don't have the language in front of me, but it basically extends the definition of a covered individual to include an unborn child. And, again, the arguments are that the way in which the legislation is written, DNA information obtained on the unborn child in the medical system effectively are considered relevant to the mother. And as soon as that child is born, then the legislation would apply already. So that the argument is that there is no window of non-coverage given the way that the bill is already written.

And this addition is unnecessary. And, of course, it raises all kinds of other issues immediately because it seems to bring another very controversial and difficult public discussion into the middle of this bill that was never intended to be a place for that debate to occur.

DR. PELLEGRINO: Dr. Hurlbut?

DR. HURLBUT: My last comment was inarticulate. So I just want to return to what I think is the heart of the question.

DR. COLLINS: All of mine were. So go ahead.

DR. HURLBUT: And I actually would like one more thing, too, and that is for you to sum up what you think we should do. But first I was trying to make a distinction between interventions very early, when we have a genetic proclivity and the later kinds of things we are used to, therapeutic interventions for existing disease.

What strikes me is that personalized medicine, so conceived as you have laid it out, could end up bordering on enhancement conceptually. In other words, sure, if you're going to intervene in something that's clearly leading linearally to a disease, that might be uncontroversial.

But then there will be other things where there will be genetic proclivities towards certain behaviors or certain dispositions of being certain combinations of your possible genomic expression. And that borders on precluding or promoting certain possibilities within your genome.

And this would come down to small molecule interventions. You know, that is where this will all go. The revolution of biology is likely to be a revolution in pharmaceuticals, not gene therapies, right?

And so what I guess I am asking you is in the broad sense, are you worried about where this kind of knowledge is taking us and how we might use it to intervene in human lives to "educate" the genome to do certain things versus others?

DR. COLLINS: That would be a very interesting discussion to pursue if we had more time to dig into it. I think we already do this in a less high tech way.

I think parents routinely are assessing the characteristics of their children and trying to figure out, oh, does this child have a particular musical ability? And if so, should we nurture that?

So they're observing the consequences of some genetic inheritance and trying to adjust what they do in terms of enhancing that child's ability to carry out certain valuable life activities.

Is it categorically different if those kinds of judgments are assisted by some kind of DNA analysis? I'm not sure it's categorically different. I'd worry that it might be seen as more reliable and that you might get into the self-fulfilling prophecy kind of outcome, where kids got early on slotted into a particular pathway of what kind of training and experiences they're going to get based upon DNA information that was actually pretty shaky. That would be unfortunate.

I mean, I guess the thing to fear here is limitation on opportunity based upon predeterministic kinds of conclusions based upon DNA analyses that should have never been taken with that much weight but somebody might try to do.

I do think that there is a risk there that we ought to think about in the longer term in terms of society, but I think we're a ways off from getting to it. And it would not be one of those where you could draw a bright line. And those are sometimes the most interesting and the most difficult.

DR. PELLEGRINO: Dr. Collins, I think I expressed the feelings of all the members of the Council, expressed our gratitude to you for being so generous in your time, responding to all of the questions in a very definitive way, and especially for opening up the whole field to us and particularly also for some of the suggestions you have made about the ideas this Council might deal with in the ethical realm. Thank you very, very much.

(Applause.)

DR. PELLEGRINO: We will now break to 10:45.

(Whereupon, the foregoing matter went off the record at 10:27 a.m. and went back on the record at 10:46 a.m.)

SESSION 6: HUMAN DIGNITY AND BIOETHICS - A PREVIEW OF COUNCIL'S UPCOMING DIGNITY VOLUME

DR. PELLEGRINO: Council members, welcome back. Council members, are we all here? It doesn't look like it. I know some are gone. Very good. Thank you very much.

This last session is devoted to the upcoming volume or anthology being put together on the subject of human dignity. Those of you who have followed the publications of the Council over the years I'm sure have seen the concept of dignity in a sense hovering over a lot of the discussion, what it is to be human, how do we preserve human dignity in the face of a variety of assaults on it today.

Council members have received papers that have been elicited from a variety of authors, some on the Council, others not on the Council. And the subject of today's discussion is to get comments from the Council members on the volume, which is being edited by Adam Schulman and is coming close to completion and ready for publication.

We have asked two of the Council members to open the on: Dr. Floyd Bloom and Dr. Peter Lawler.

And while they're heir comments and throughout the rest of the discussion, I wa ge other Council m embers if they wish to take the invitations being ex o write a comment on one of the existing papers, which you have read, or submit a paper of your own. We would like as much as possible to have Council participation as well as the participation of invited authors.

Let's begin, if I may. Dr. Floyd Bloom, would you lead us forward?

DR. BLOOM: I hadn't been appointed to the Council when you decided to do this compilation of essays on dignity. So when Dan asked me to start the discussion of the essays by Gil and by Dan Dennett, I looked at it as a great learning experience.

Reading Gil's essay gave me the chance — in fact it required — that I go back and read parts of Human Cloning and Human Dignity, Being Human, and Beyond Therapy.

A skeptical Council member might wonder whether getting new Council members to read old Council reports is not a major part of how you get picked to lead discussions.

(Laughter.)

DR. BLOOM: If that were the case, thank you because I learned a lot. And I thought these were both thought-provoking essays.

When I moved from the NIH to the Salk Institute in 1975, I was given the study of Jacob Bronowski, who had just died. And it's Bronowski's writings that come to mind, especially The Sense of Human Dignity, when I ponder the phrase "human dignity."

But the Council's early report, as Gil so clearly notes in his essay, Bronowski used the term "human dignity," but, as far as I can tell, he never defined it except by examples of respect within the community of scientists for each other's findings and interpretations, whether or not one agreed with them, and the scientific spirit to dissent and explore while searching for truth as human values, which in his phrase he said were "ratified by the great religions of the world."

He said the outcomes of science and technology are mere tools and artifacts, it's the spirit and creative energy behind them that form the basis for human values and ideals, which is as close as I think I could find that he came to talking about human dignity explicitly. And it's that spirit that I think of when I ponder the meaning of dignity in the sense of this volume and these two particular essays.

Gil's essay refers to the three definitions of dignity described by Beyleveld and Brownsword and more recently by Caulfield and Brownsword in their considerations of policy-making for the era of biotechnology. Those three definitions are: number one, empowerment, which is very similar to what Mike said yesterday, the right of individuals to make autonomous choices; secondly, as a means of constraint; and, thirdly, as dignified conduct.

So since Gil is here and I can pose the query to him, it seems to me that you use dignity as constraint in a fashion somewhat differently than do Beyleveld and Brownsword. You used it in the sense of constraint in a legal or ethical issue to control activity to which one freely consents and which seems to harm no one. But Beyleveld and Brownsword used the sense of scientific constraint in the terms of barring activities, such as cloning humans or selling organs for transplant, as a social position that these forms of scientific activity are against human dignity because they are contrary to the public good. And that seems to me much closer to the way I read Leon's essays to have defined or used the phrase "human dignity."

Dr. Dennett's essay that we already engaged in a little bit of discussion earlier this morning is much closer to neuroscience. And so I feel more akin to it. And it uses the recent findings with non-invasive imaging on which to build the case that human dignity arises — and this is his list — from the capacities of the human brain that allow for language, art, music, religion, humor, recording and reviewing history, and planning projects that go well into the future, and that humans are the only animals that can conceive of the project of leading a good life.

Studies that begin to disclose the parts of the brain that work together when we make decisions that attribute trust and emotional status to others ground for me in real substance these brain-based human abilities that lie at the heart of human dignity.

One might also expand on his concepts of dolphins and great apes as having a protomorality, a capacity to cooperate and express altruistic behaviors. Elephants, for example, have recently been shown to be capable of mirror self-recognition and altruism, not only for their own species but for

other species. And recent news stories again substantiate the idea that dogs will willingly rescue human beings, even if they don't know who those human beings are.

For the most part these two essays, both very thoughtful, taking their own levels of resolution do not directly contradict each other except for the one exception that Robbie pointed out in his questions to Francis Collins.

On page 6 of his essay, Dennett asks whether the very meaning of our lives depends on the reality of our immortal soul. And he answers no. Well, Gil on page 11 takes the view that society's commitment to equal dignity is best and most safely grounded in religious belief.

So if Dr. Dennett had been here this morning, what I would have liked to have asked him is this. I know or I can imagine how the human brain does language and music, remembering and planning. And when I queried PubMed about brain imaging and religion, much to my surprise, there were more than two dozen papers that use positron emission tomography, functional MRI, EEG, even SPECT., to look at phenomena from the mystical experiences of Carmelite nuns to buddhists contemplating a remembered meditation.

So, not surprisingly for those who understand that interpretation, there are certain parts of the brain, particularly on the right side of right-handed people, that show enhanced activity during religious experiences, but what Dr. Dennett doesn't tell us is what brain systems or networks he thinks underlie religious contemplation and what in our evolutionary history has given rise to a system that would mediate such functions.

That's mostly what I have to say, but I would like to offer this for the Council's amusement after this lengthy discussion. This is the final version of Bob Dylan's song "Dignity" from 1991, "So many roads, so much at stake, so many dead ends, I'm at the edge of the lake. Sometimes I wonder what it's gonna take to find dignity," 1991.

DR. PELLEGRINO: Thank you very much, Floyd.

For the benefit of those who have not seen these papers, we asked our discussants to look at two of the papers, particularly that will be appearing in the volume. One is Dr. Gil Meilaender's "Human Dignity: Exploring and Explicating the Council's Vision" and another by Daniel C. Dennett, "How to Protect Human Dignity From Science."

Now for our second discussant.

DR. LAWLER: Well, thank you. And I will try to be brief, given the lateness of the hour.

So my job is to introduce these two papers by Meilaender and Dennett. And I will use the last names because I don't know Dennett.

From one point of view, they defend two extreme and incompatible positions. They're both extremists.

(Laughter.)

DR. LAWLER: As was pointed out in the last session, Dennett is surely an extreme atheist. And Meilaender we might say is an extreme theist; that is, an Augustinian. But extremism in defense of dignity is surely no vice.

(Laughter.)

DR. LAWLER: And they are both, as they say, nice guy extremists, although you can find a sentence or two in both articles like the one Robbie quoted last session, which are overly assertive and a little bit mean.

In general, these dignity extremists lack the self-righteousness that often accompanies dignity extremism. So they agree. And they agree. As extremists often do, they agree on many things, more things that it appears at first. They both agree that dignity is not a useless concept. And this is not a small point of agreement.

And they both agree that dignity has to be saved from modern science or at least misunderstandings of what modern science actually teaches. Not only that. They seem to agree that our understanding of dignity, at least our traditional understanding of dignity, is Christian.

So Meilaender says that the dignity of each unique and irreplaceable human person is real. And the

only explanation for that observed phenomenon of human dignity that makes sense is the Christian one. So our belief in the equal dignity of all human persons is part of our Christian inheritance.

Dennett agrees that our understanding of dignity or at least the traditional understanding of dignity, the given understanding of dignity is Christian. But he adds that the Christian claims about the soul or some immaterial dimension of personal existence have been refuted by modern science.

So dignity has now the same status as the mermaid, although I would add: sensible people never believed in mermaids, although sensible people in the past I think believed in the soul.

Dennett adds — and this is very important — that our need to believe in dignity is real and characteristic of the type of social being human beings alone are.

We social beings, who conceive a project for the good life to live good purposeful lives, good lives, can't live together well without believing in some useful illusions, like free will, love, and dignity, but free will, love, and dignity, strictly speaking, have no real basis in what we can actually know about our accidental evolutionary and wholly material existences.

So Dennett's ingenious solution that solves the problem of the incompatibility perhaps of dignity and modern science is to say today we should candidly admit our need to believe, that we're hard-wired to need to believe. And then our allegiance to the belief in human dignity will be supported by the good life it makes possible for us.

We can see that if we give our allegiance to dignity, our lives will be better. So we can suppress the thought about whether our belief in dignity actually makes any natural sense because we can't see. According to nature, we do believe. And when we do believe, we're better off as a certain singular kind of social animal.

So a difference, a major difference, between the two great thinkers we're talking about is that for Gil Meilaender, it would make all the difference in the world. We really are unique and irreplaceable beings. Dennis suggests we can suppress that thought about the reality of the situation and regard that thought as a useful one.

So for Meilaender, our dignity is mysteriously given to us by a personal god. And the human situation is fundamentally mysterious in certain respects without a religious explanation at least.

For Dennett, nothing human is mysterious. Everything can or will be explained in a wholly material way. That's good, though, because then we can understand scientifically why we have to attribute dignity to ourselves. Insofar as we believe our dignity is mysterious, we can't consciously and rationally employ it for the purposes of flourishing social life. So modern science, properly understood, makes dignity more effective.

There are other points of agreement between these two extremes. Meilaender and Dennett don't agree with those who connect dignity with autonomy, with our freedom from our natural limitations for laws or choices we impose on ourselves.

Autonomy is based on the denial of the truth about our embodied existence. And dignity, properly understood, should be compatible with what we really know about our limited social and temporal lives.

Even Dennett's fictional dignity depends on our understanding of our real material situation. So for both Meilaender and Dennett, dignity is a characteristic of embodied beings who know the truth about their situation. Not only that.

These two extremists both have an egalitarian view of dignity, separating themselves from, say, certain members of this Council, who have a more aristocratic understanding of dignity.

They deny that our dignity is dependent on the excellence or virtue we display in social context. It's easy for Dennett to do that because there's nothing I can do that will really make me more dignified given that I am not really dignified anyway. And Meilaender says there is nothing I can do that can really make me undignified. So Meilaender says it's true, and Dennett says it's useful to regard all human beings as equally dignified.

We have to wonder whether either Meilaender or Dennett really disconnect dignity from real human achievements in thought and action. Meilaender criticizes Leon Kass for saying patients because they lack agency lack the capacity to be dignified. And to support his case, he gives us the example of a dignified patient who acts with patience in light of the truth about his dependent human condition.

So in a very Christian way, he explains how patients can be more dignified and more truthful than great leaders or manly or magnanimous men who have forgotten about the limitations of their embodiment.

But Kass responds that in describing the patient, the dignity he displays depends upon action and thought appropriate to a situation. So the patient, Meilaender describes, is not really a patient. He's just part patient and part not because a pure patient would be perfectly passive.

So a pure patient would be someone with advanced stage Alzheimer's, lacking any capacity for thought and action. But an advantage of Meilaender's and Dennett's position over, say, the position of Kass is they can explain quite clearly why patients with advanced stage Alzheimer's, late stage Alzheimer's, have dignity.

Meilaender says they have dignity because of the type of being they are and cannot change. Dennett might say, at least, it's just socially useful to regard people with late stage Alzheimer's as having equal dignity; we'll have a better life as a result. Kass actually has to think about this. And it's hard because he doesn't regard dignity as given in either of those two ways.

Now, I would make one more point. Meilaender and Dennett connect dignity with degradation, Dennett almost in spite of himself. Indignant behavior is or anti-dignity behavior is reducing human beings to less than they really are.

So Meilaender has told us that a human being who alienates his body or alienates himself from his body through the sale of his kidneys is acting in an undignified way. And even Dennett worries that a misinterpretation of modern science will erode our indispensable faith in human dignity.

So they both really want to preserve the qualities that really distinguish human beings from their attack by modern science in some way or another. So surely even Dennett wants to preserve the real existence of human beings capable of acting in a dignified way from, say, biotechnology that would suppress those parts of the brain that make dignity indispensable.

So they both show us why we should use the word "dignity" because that's not self-evident because Americans in most of our history have spoken not so much of dignity but of rights. Because we can speak so clearly of rights, why go down the murky road toward dignity, which is controversial and causes us to be self-righteous. Here's why.

The Twentieth Century and the Twenty-First Century. The word "dignity" made a comeback in the Twentieth Century because what the totalitarian regimes did in the war against the reality of human nature was a lot worse than a violation of rights. So you can't say Hitler just violated rights. You can't say Stalin just violated rights because they were at war against the being capable of experiencing dignity, human individuality.

So the great dissident opponents of totalitarian regimes, like Solzhenitsyn and Havel and Pope John Paul II, were big on bringing back the word "dignity" because the word "rights" just wasn't enough.

And in the Twentieth-First Century, great men like Leon Kass bring back the word "dignity." By replacing "life, liberty, and the pursuit of happiness" in a crafty way with life, liberty, and the defense of dignity because what biotechnology could conceivably do to us, misapplied, would be at war with the very aspects of our nature that allow us to be dignified beings because biotechnology opens the opportunity of actually changing our natures in an undignified way.

So I think even Dennett in his own way agrees with that. We have to have the use of the fiction of dignity to fend off biotechnology that might do that. But I would add to everything these great experts say another piece of evidence of our dignity is that both totalitarian efforts and biotechnological efforts to eradicate those aspects of our nature that make us dignified beings will inevitably fail.

Thank you.

DR. PELLEGRINO: Thank you very much, Peter.

Gil, would you like to respond?

PROF. MEILAENDER: Let me just say a couple of things. Judy Crawford was already nailing me at breakfast with some questions about my essay. And I told her I was just going to refer all questions to her. That would be my preferred strategy, actually.

And also I don't myself think it would be a fruitful discussion for sort of me just to respond to

questions. I think the Council should have its own discussion.

Let me say a couple of things. Floyd directed a specific question. But I wasn't sure I understood it, Floyd. Let me say a word. And you'll just have to see whether I got you or not.

I took the second notion of dignity from B&B, as I like to call them since their names are not easy, the side constraint notion, to be at least somewhat similar to the notion I had developed in the last part of my paper about dignity as a kind of anthropological position or dignity as serving as a placeholder, as I called it, for a richer anthropological view but only somewhat similar to that in the sense that theirs is largely a negative notion.

The language you quoted I thought was less mine than their view in a way, just autonomous action that harms no one and so forth; whereas, it seems to me that the anthropological vision that I had tried to show the Council at least attempts to develop, though it will have some of those negative functions that serving as a side constraint is an attempt, actually, to say something more positive about what really makes human beings human beings. So that would be sort of what I would say to that.

Then just a word, drawing on Peter's various comments. If I had this to do over again, I think I would reverse the parts of the paper in a way because I think it might make more sense.

See, I tried to sort out what I think are several different things the Council does with the language of dignity in those reports. And then I worry about certain issues that they raise.

The second general thing that I sort out, what I was just referring to, what I call sort of a placeholder for a richer understanding that comes out at certain places; in Beyond Therapy in one way; certain places in the cloning report in another way; certain places, actually, in the little introductory comments in Being Human, the reader, as I noticed.

I wouldn't have said — now, I'm subject to being corrected. I wouldn't have said there was anything necessarily Christian about that claim of mine. I would think there might be various ways to get to that anthropological view. I probably get to it in certain theological ways, although there certainly have been Christians over the centuries who have sort of fallen short of that view, at least by my lights.

So I don't know. You know, if you had reason to prove to me that it was necessarily Christian, that would be okay with me. That wouldn't bother me, actually. But I don't think it is. And I don't think I developed it that way.

The first kind of issue I worry about, which is where the equality issue really comes out, that is where I argue that I think, in fact, we have been dependent on the religious tradition in a certain way to be able to affirm the equal dignity.

So I think that the development of those two aspects, the second one is more kind of the dignity of human nature, the nature that we all share. The first is the dignity of the person, the individual person, who, though belonging to the species, may have some of the characteristics of our nature and not others of them. And I think if I had it to do over again, I might have reversed the order of them in order to try to make that clearer.

But that much I would say at least by way of trying to clarify the sense in which there are or are not specifically religious or theological claims at work. And I think I'll stop there.

DR. PELLEGRINO: Thank you very much, Gil.

I'll open the subject to general discussion now. It need not be limited to these two papers, any of the papers that you have read in the anthology that Adam has put together for you up to this point. Dr. Schaub?

PROF. SCHAUB: Yes. I do have questions for Gil, even though he doesn't want questions. It will take a while before the questions emerge, and I want to ask your forbearance. I started jotting down some notes on Gil's essay, and I got a little carried away.

Since I am usually pretty brief, I hope that I have some accumulated minutes and that you will bear with me as I sort of deliver myself of this. Well, I don't know how to characterize it. I'll just launch into it.

Gil tells us in his fine essay that there are some realms in which comparative judgments of excellence are permissible, indeed required. Assuming that our consideration of these two papers is one such

venue, I feel at liberty to direct my remarks to the more worthy of these papers and to ignore the other.

Gil argues that Christianity has transformed the Greek emphasis on comparative dignity. Christianity, he says, marks 'a great rupture in Western culture.' He further argues that this Christian egalitarianism is the inspiration behind the American assertion of man's equality in the Declaration of Independence. He suggests that one needs belief in the fatherhood of God for the brotherhood of men to be seen as self-evident.

And he worries that with the decline in religious belief and maybe even more especially the unwillingness to acknowledge the connection between religion and politics, we're increasingly in a situation where our commitment to equal human dignity is ungrounded and, hence, unsustainable.

So Gil wants us back on firm ground. And, in particular, he argues that there are two places where differences in excellence or dignity must not matter. The first is at the threshold of death when the continuance of life itself is at stake. And the other that he mentions is the opportunity to live within human society and participate in its common life.

Now, while Gil makes plain his discomfort with the Hellenistic, aristocratic take on dignity— he even calls it a temptation that ought to be resisted — I felt that there were many instances in which Gil was more of a Hellenizer than he admits. And let me cite just one of those.

Early in the paper Gil presents us with a character from a Galsworthy novel. I think Gil is probably the only person in the nation still reading Galsworthy.

(Laughter.)

PROF. SCHAUB: I mentioned this to a literary critic friend of mine. And she said, "Galsworthy. How stodgy."

(Laughter.)

PROF. MEILAENDER: I read it many years ago.

(Laughter.)

PROF. SCHAUB: In the Galsworthy novel, Gil offers us Old Betty Purdy as an individual who confounds our aristocratic assumptions about greatness and dignity. And the passage that he cites does indeed show the falsity of status and wealth as markers of human dignity, but I think it does not at all argue for equal human dignity.

The greatness of this little old lady came from the moral virtue she displayed in the midst of the ordinariness of her life. Her greatness depended on her comparative excellence, not her equal human dignity.

We're told of the meagerness of her material existence and her limited range of action, but her back had been straight, her ways straight, her eyes quiet, and her manners gentle.

I take it that we're to admire her fortitude and her probity and her kindness. Those are not qualities equally possessed. If the woman had, instead, lived in Buckingham Palace and had the world as her stage, real greatness would still have depended on her moral virtues.

I think that's one of the points made by the wonderful movie The Queen starring Helen Mirren. Of The Queen also, it could be said that her back had been straight, her ways straight, her eyes quiet, and her manners gentle.

Now, although Gil reiterates that he finds something offensive about the aristocratic view of human dignity, it seems to me that he himself regularly recurs to a version of it and that he can't help but do so. After all, in Christianity, the message to respect basic humanity came from the fullest humanity. The bearer of the message was not just a godly man but God become man. We are to imitate his perfection. Christian virtues may be different from classical virtues, but the standard is — if anything — higher.

Gil appeals to Lincoln for evidence of what he calls the problem we have with an inegalitarian concept of dignity. I, too, accept Lincoln as an authority. However, I don't think that Gil reads him quite right.

Lincoln is not at all offended by the aristocratic view. In fact, Lincoln always starts his explications of

the meaning of the Declaration by acknowledging the fact of human inequality. Men are not equal in all sorts of features and capacities. And Lincoln lists a number of them.

But for Lincoln, admitting the existence of those various politically and socially significant inequalities should not in any way imperil the real truth of the Declaration, namely that men are equal in their natural rights to life and liberty.

And note, as I think others have already mentioned, Lincoln speaks of equal rights, not equal dignity. I suspect that we may have gone awry when we confounded the language of dignity with the language of equality.

Dignity was not a word that either the founders or Lincoln employed much. And when they did, it was in a, frankly, meritocratic sense.

Moreover, in the passage that Gil cites, I think it is worth noting that Lincoln illustrates the equality of rights by saying that human beings are equal in their right to eat the bread that their own hands have earned.

In other words, even this equal right hinges on earning. Labor is the title to property. And men will labor unequally. Now, Lincoln doesn't tell us here what those who are unable to labor are entitled to.

And I surely don't mean to suggest that Lincoln would have denied sustenance to the young or the elderly or the sick. Lincoln was attacking the injustice of slave labor. And his arguments are marshaled accordingly.

And we certainly have evidence of Lincoln's capacious humanity in the closing lines of the Second Inaugural, when he calls on Americans to care for him who shall have borne the battle and for his widow and for his orphan.

But the example of Lincoln leads me to think that we have a model for how to combine and celebrate both the respects in which human beings are equal and the respects in which they are unequal. And one need not imperil the other.

Indeed, the life of Lincoln, a superior man, who devotes and sacrifices his life to the teaching of equality, reminds us that we can't have one without the other. So we shouldn't lose sight of the success of the American founders, among whom I include Lincoln, in combining the egalitarian and the inegalitarian. They just didn't seem to struggle with it as we are.

I was a bit taken aback by Gil's assertion that there are two places where comparative judgment should not be given any scope: at the threshold of death and participation in human society. Gil seems to say that these are absolutes, but I wonder whether he really means it.

The quote from Kierkegaard says, "If you save a person's life in the dark thinking that it's a friend but it was the neighbor, this is no mistake." Well, it seems to me it might have been a very big mistake if your neighbor also happened to be your enemy and you happen to have been on a nighttime reconnaissance mission. In other words, Kierkegaard's statement is radically apolitical. It abstracts entirely from the distinction between friend and foe.

Gil, do you mean that one is never justified in taking human life, not even the life of an enemy in combat? If comparative judgments have no place at the threshold of death, does that commit you to not only oppose the death penalty, which I take it that you do, but commit you also to a thorough-going passivism?

If, on the other hand, you allow for individual and societal self-defense, then it seems to me that you have admitted the validity of comparative judgments of worth, even at the threshold of death. So in this case, it seems to me that the language of equal rights is preferable to the language of equal dignity.

Rights are inalienable, but they also imply reciprocity and responsibility. Those who violate the rights of others have rendered some of their own rights forfeited. So that a rights-based approach protects the innocent and the weak, about whom Gil and all of us are concerned. But it doesn't require us to abandon human judgments about virtue and vice.

As to Gil's claim that our founding doctrine is grounded in Christianity, it's true that the Declaration refers to man is created equal and endowed by their creator with certain inalienable rights.

It's also true that Jefferson shared Gil's worry that once religious belief falters, the commitment to equality will be hard to sustain. Here's how Jefferson put it, "And can the liberties of a nation be

thought secure when we have removed their only firm basis, a conviction in the minds of the people that these liberties are of the gift of God, that they are not to be violated but with His wrath?"

Having granted that much, I would just point out that the Declaration refers to the Laws of Nature and Nature's God. And I suspect that nature's God is not quite the same as the biblical God.

Gil says that the truth of human equality is a theological proposition or theological assertion, but how strong a theology is required? Is natural theology sufficient? Jefferson I think thought that it was.

And in other writings, Jefferson argued that it was not religion at all but, rather, reason and science that will reveal the truth of the Declaration. In a letter written just days before his death, Jefferson said, "All eyes are opened or opening to the rights of men. The general spread of the light of science has already laid open to every view the palpable true that the mass of mankind has not been born with saddles on their backs, nor a favored few booted and spurred, ready to ride them legitimately by the grace of God."

Now, as we know, even if equal rights are self-evident, they're not self-establishing. The paradox of rights is that you have to hazard your life and liberty in order to vindicate your right to life and liberty.

As Frederick Douglass never tired of telling his enslaved brothers, "Hereditary bondmen, know ye not who would be free themselves must strike the blow."

This was a heartening message for blacks and for women, who had the wherewithal to strike the blow and secure the dignified treatment to which they were by nature entitled.

It may not be such a tearing message for the young or the drastically impaired, although perhaps the answer that Locke gives about the young is sufficient. He says, "Children I confess are not born in this full state of equality, though they are born to it. Consequently, our handling of them must always be aware of their directedness toward rational liberty." Children are rights bearers, too. Accordingly, the power of parents and guardians is limited."

Locke insists it does not extend to life and death. Immature human beings, embryos included arguably, have the same bodily immunity as adults. There's a fundamental human right not to have one's body captured or controlled by others for their ends and purposes.

In the case of the weak and immature, respect for this basic right to life will continue to depend on the deference of the strong. In his speeches, Lincoln deployed his relentless logic to get those who had the upper hand to realize the momentary and fragile character of their strength. He stressed that the only guarantee of one's one rights lies in the recognition of the rights of others:"As I would not be a slave, so I would not be a master."

And, again, in giving freedom to the slave, we ensure freedom to the free, honorable alike in what we give and what we preserve. This is a version of neighbor love and brotherhood that is reasonable and republican in character. It doesn't deny the fatherhood of God, but it doesn't draw attention to it either.

And, in closing, at the risk of impiety, I will suggest that brothers can get along pretty well when the father, whether human or divine, remains further in the background. After all, the first story of brothers in the Bible is a story of fratricide in response to God's favoring the gift of one brother over the other. I'm not so certain that it helps our sense of human equality to view matters under the aspect of eternity.

As I read the Bible, some of us will be eternally damned and others saved. We are not equidistant from God, either here on Earth or later. I'm quite certain that Gil is nearer my God to Thee than I am, but I think that we can still be equal citizens, mutually acknowledging our individual rights and brotherly responsibilities.

DR. PELLEGRINO: Thank you very much, Dr. Schaub.

Gil, do you want to comment?

PROF. MEILAENDER: Sure. I'll comment on a few things, not by any means everything that Diana has taken up. Just a comment on what I drew from my stodgy reading habits, I read all nine volumes at one time in my life.

Although, Diana, you are always a very careful reader, I didn't think you did quite justice to the way I used the Galsworthy passage there. That paragraph where I used it begins, "Suppose, however, that

our understanding of comparative excellence were reshaped somewhat by a sense of equal human dignity."

And having quoted, I say, "And suddenly what seems almost a given in the Council's discussion who are the great and who are the ordinary human beings may be far less obvious." I wasn't trying to rest the entire argument for equal human dignity on that but simply to begin to reflect on the significance of a kind of democratizing of that concept that takes place.

I mean, the argument moves on from there. It doesn't stop there. So that I think you, careful reader though you are, abstracted that a bit from the flow of the argument and just let it stand on its own.

A second point, I don't know if you really want to argue theology or not, but if you would like a discussion of the concept of incarnation, we can have it.

Jesus is not thought to have the fullest humanity in any sense, whatever that might mean. He's thought simply to have assumed our nature into God's own nature, the nature that we all share but not a fuller sense of it in any way. So that, I mean, I don't think that's right.

The Kierkegaard stuff, the neighbor for Kierkegaard is anyone whom you may encounter. And, therefore, if you rush into the burning house next door thinking to save someone whom you really like who is, of course, your neighbor most fundamentally because the most fundamental category is neither friend nor foe but neighbor, you rush in, save someone whom you really like, drag the person out to safety, only to discover that it's someone you have never met or someone you hate, Kierkegaard says in the most basic sense you have made no mistake. You ran in there to save your neighbor. You saved him. And I think that's true.

That doesn't mean that friend or foe distinctions make no difference at all in life. It doesn't mean — I mean, you raised the issue of combat, for instance. We may, alas, find ourselves in circumstances where the needs and the claims of several neighbors seem to stand in conflict with each other and we have to decide whether there is any way to serve the needs of any of those neighbors at all there.

Many people, myself included, have been drawn to some form of just war thinking in those circumstances. I mean, even the neighbor against whom you turn has certain claims on you. There are certain things you can't do at that point. But it's an attempt to find a way through that sort of conflict between the claims of neighbors.

There have been some people, of course, who have thought that you just shouldn't do anything. I don't myself think that, but I think that what one seeks there is — I mean, when the claims of several neighbors conflict, justice is what one tries as best one can to do in sort of defending not oneself but some other neighbor who is in need.

And then, finally, on the kind of, really, I think larger — the issue that is really at the heart of what you say, well, you know, I like to honor the founders, too, but I do not bend the knee before them.

The American tradition is larger than what the founders alone had to say. There was a tradition here before 1776. And that larger tradition, which has continued to be mined, as you surely know, by political theorists since then — I mean, think of Cary McWilliams' idea for eternity in America, for instance — would suggest that there's a whole lot more to our tradition than simply that language of rights that in the context of struggle for independence came to the fore.

But the larger issue here for me would be that, I mean, I'm not sure what the thrust of your appeal to confine ourselves to the language of rights is. For better or worse, we happen to have used dignity, as I think — I mean, whatever you think of my particular claims, I mean, I tried to sort through the material we used in order to say things we wanted to say about the nature of human action and how it relates to enhancement and about human procreation and so forth. We didn't find the language of rights sufficient to do that.

I point to some examples of this along the way. And I guess before I took that back, I would need to see an argument that suggested that the language of rights could accomplish what we tried to accomplish and what I would still think is important to accomplish.

So that, you know, as I say, the things that we did in Beyond Therapy and The Cloning Report seemed to me to at certain places make use of that language in important ways that probably can't just be duplicated by rights language. And it's, therefore, language we need to say if we want to say everything that we need to say. That would be what I would say.

PROF. SCHAUB: Yes. Just very quickly to that, I don't think I was arguing for a return exclusively

to rights language but, rather, a combination of equal rights and earned dignity so that when it comes to these issues sort of at the beginning of life and at the end of life, I really do think that the rights language may be sufficient.

And it was revealing to me that where the dignity language really becomes more appropriate is in the Beyond Therapy report and especially in the section on performance when you're talking about, you know, the essential dignity of human action. That's why I had no quarrel with the section of the paper that dealt with the anthropology. That all seemed to me very fine.

PROF. MEILAENDER: I would just note that it is not the only place where we — I mean, the Taking Care volume uses it also. And it's not that kind of anthropological principle at work there.

PROF. SCHAUB: I am just saying I think it is more appropriate in that one context than in the other context.

DR. PELLEGRINO: Thank you both.

We will now open the discussion to other members of the Council, not necessarily on these papers, on any of the papers in the anthology. Dr. George, I saw your hand first.

PROF. GEORGE: Thank you, Dr. Pellegrino.

Gil, I think that there are two beliefs that are the glories of our civilization and central to our political self-understanding, our national political self-understanding: the belief in the inherent dignity of the human person and the belief in the equal dignity of all human beings.

Now, as I say, those are glories of our civilization, but they are also problematic and puzzling and difficult to explain because we know of the profound differences between persons. And we know that there are some persons who are in severely debilitated conditions with respect to those very features of our humanity, which seem so central to its dignity and its specialness. And so we struggle to make the argument in defense of inherent and equal dignity.

Now, it seems to me that there are two ways of making the argument. I don't think they are incompatible. And at the end of this, I'm going to ask you the question whether they're incompatible and we have to choose.

One way is to make it the way I think you are making it, drawing on the great moral theologian Oliver O'Donovan, among others, where one is arguing from the theological proposition that there is a God and that man is made in his image and likeness to the conclusion that man, therefore, bears an inherent dignity and all men have an equal dignity, equal share.

The other way goes in the opposite direction. It is to observe that human beings as possessors of the God-like powers of reason and freedom, literally awesome powers, that are traditionally associated with divinity have a basic dignity, an inherent dignity, and that since all human beings possess, in at least radical root form from the beginning to the end, this basic natural capacity, — it may be blocked in the case of a severely debilitated, congenitally debilitated, person or something like that, it might be locked, but, nevertheless, at least in radical form, it's there — we acknowledge that people have inherent dignity, we're all equal. And then we raise the question, well, how can it be that we material creatures possess these powers that are not even reducible to material causes or so it's supposed?

Dennett would disagree with this, but many of us would think that they're not reducible and a complete account can't be given in purely materialistic, reductive terms. How can that be?

And then we ask whether it might be in virtue of a more than merely human ground or source of these realities in the whole of the intelligible order, which has given us some share, limited to be sure, and fallible, but some share, in those powers of reason and freedom, those divine, awesome powers, the powers that are at the heart of our dignity.

And so in the second way of arguing, the argument is not from God but, rather, to God. You might put it this way. And I'll conclude. What does it mean to say, as the Bible says, that man is made in the image and likeness of God? It obviously doesn't mean that God has two hands and five fingers on each hand and so forth. Doesn't it mean that man possesses in limited form but, nevertheless, really these God-like powers, that God has made man in his image and likeness by giving him a sharing in these divine powers of reason and freedom, so that you can say it in theological terms and quote Genesis or say the same thing in philosophical terms that don't divert to the theological question but are not incompatible with it or are they?

PROF. MEILAENDER: I'm moved to reflect again what an unusual government body this is.

(Laughter.)

PROF. MEILAENDER: And I apologize for whatever responsibility I bear for that fact.

(Laughter.)

PROF. MEILAENDER: Let me ask you one question before I try to answer. Would I be right in assuming that you are more drawn to the second of those two styles of argument?

PROF. GEORGE: Only by temperament.

PROF. MEILAENDER: Okay.

PROF. GEORGE: So that I would say I'm not saying that one is more legitimate than the other or more compelling than the other. Floyd is a scientist. Janet is a scientist. I do legal philosophy. I am more inclined toward philosophical things.

I think theologians are wonderful people and so forth and so on. And I am happy to see them do business their way the way I am happy to see Floyd and Janet practice their crafts. But by temperament, I do it the other way.

What I am really interested in asserting unless I'm wrong, in which case I want to be corrected, is that they're not incompatible.

PROF. MEILAENDER: Okay. No. That's fine. Well, you know me. I let 1,000 flowers bloom. And I have no objection to working in either direction. And I do think that they are in principle compatible, though I probably have less confidence in how well the second route will work than you may have.

And I think, just as a matter of fact, that the concept of the image of God is a really muddy concept, both biblically and in the sort of history of theological reflection on it. I mean, it's just not clear anybody knows for sure what it means. So that in terms of the steps by which you have proceeded there, I mean, I think they would be complicated.

I probably in this paper proceed a little bit in the other way because there is a certain point where it seems to me it's useful, rather than thinking of religious folk as always on the defensive and having to make the case for saying anything about what they believe in public discussions about matters like biotechnological concerns, it seemed to me useful to say, "Well, for better or worse, these religious folk have got a reason to affirm something that most of us claim we want to affirm, the equal dignity of human beings. And, you know, if you want to affirm that and you don't share that reason, well, then, you know, come up with another one."

It's not that I object to somebody coming up with other ones, though I'm inclined to doubt that there are just a lot of them floating around that will be successful.

But, I mean, I was concerned to make the point that this has functioned as a kind of ground for that view and has a certain kind of legitimacy to function that way in our discussions.

But certainly I don't expect everybody to want to start with theological premises. I understand that. And if one can provide a kind of reasoned argument that gets to the same place, I am happy.

You know, I take my friends wherever I can find them in life. It's not easy. And, you know, I am happy to get support from wherever it comes.

DR. PELLEGRINO: Thank you, Gil.

Leon?

DR. KASS: Thank you.

I am really in a way reluctant to enter after these really very eloquent and carefully prepared responses, you know, two by assignment and then this stunning and I think very powerful critique, Gil. But let me say something about your paper.

I think it has done an enormous service by going through the work of the Council's previous reports and shining your bright light on acknowledging the conceptual difficulties and even confusions that

sometimes emerge if you sort of took the various places where these placeholders sit for certain notions and to call attention to the central difficulties of the concepts and the not always fully clear use that we have made of them in those reports while at the same time defending the necessity of using such notions in those particular places where nothing else would seem to do.

Second, I think it's a great contribution to call attention to the insufficiency of simply laying down along side by side some notion of the dignity of full flourishing and some notion of the equal dignity independent of flourishing.

You can say you were in favor of both, but if you simply are doing that, you haven't really articulated their relation. And it is I think an ongoing challenge for those of us who I think without self-contradiction — and Diana has given a wonderful example in the person of Lincoln and the kind of sympathies that we can have for that. It's not a contradiction.

And, nevertheless, I think that it's incumbent upon us to try to give an account of how the first and the second are related, the second is related to the first. And I took that to be, really, my assignment in struggling with this for the paper, which belatedly came to all of you only recently.

I can't resist. This is as an aside and not for comment. The title of the paper is "Explicating the Council's Vision." And, for the record, I would simply say it's one man's explication of the vision insofar as it's there.

And to the extent to which my own personal views are analyzed in this particular paper, every author complains that he or she has been misunderstood. And I concede that one contributes to such misunderstanding. I'll simply say on the personal side let my own essay be an attempt to deal with what I take to be the not quite accurate presentation.

On the substance, you talk about in a certain mood we feel a certain inclination to think this way, that there are certain temptations that we might feel to make judgments about the lives that people live or whether they are degrading themselves or are somehow demonstrating certain qualities that we admire.

I don't think that you would want to say of Thomas Aquinas that his argument about dignity was based upon his being in a certain mood or he yielded to a temptation to which he should not have yielded when he made that comment that you quote.

There are philosophical reasons. Diana has done a really nice job. Peter has done a nice job, I think, for talking about the virtue component. And that leads me to the second argument, and I have done something of this in my current paper.

I think you're mistaken to say the essence of the notion of the dignity of a virtue, let us say, or of good deeds — and they are good deeds in the small — is that they are comparative. It's only accidentally that these are comparative.

If every single human being behaved courageously, it would still be dignified, even if there were no inequalities. And I think that you do not have to embrace inequality in order to recognize the excellence. What you're measuring are the deeds of human beings against the standard of worthiness, not compared to one another.

The sports example is comparative necessarily because there are winners and losers. The virtue example is only accidentally comparative, would that there were less grounds for making that comparisons and people lived up to the standard, but I don't think that you have to somehow fear that because unavoidably we will wind up saying certain people are vicious, that the judgment of virtue depends upon one person being better than another.

I guess I don't want to go on much longer. Well, two more comments. I do think that there is a real fear that if you begin down the road of acknowledging the dignity of a virtue of flourishing, that you might be put in a position of making invidious judgments at the edges of life, when nobody wants to do them or at least decent people shouldn't do them. And if your concern is about the death and dispatching question, then the equality principle is absolutely crucial.

On the other hand, if your major worry is about degradation, dehumanization of the sort that several people have spoken about, it will not do simply to make a plug for the principle of equality because one could be equally debased and not know it.

So I think depending upon which part of this bioethical discussion you're most worried about or which is most on the table, these two different notions deserve a place.

And then, finally, — and I don't endorse either of the two alternatives that Robby has given us. It seems to me that I don't think there's a word that has been written in any of the documents that this Council has produced that depend for their arguments on human dignity on any particular theological view.

It might be that as individuals, that we come to these things, but we have tried to have these discussions in terms of arguments and persuade one another on the basis of a kind of public reason, nor do I think that there is any notion about the dignity that has been discussed here that rests upon a metaphysics of the immortal human soul.

You might want to suspect some people of believing that. For the record, I am not one of them. So I don't think that — we have tried to sort of start with human phenomena. We don't necessarily care whether it reaches to metaphysics or theology.

We're trying to appeal on the plane of the moral concerns that we now face in our practical decisions and as our life is unfolding under the new developments in biotechnology.

And it seems to me it's very important. I mean, I don't mind. In fact, I welcome the fact that the Christian thinkers don't hide their lights under a bushel. I think that's very important.

On the other hand, if you want to say, "Look, the arguments for the equal dignity of human beings depends upon that teaching," we're, in effect, saying to other kinds of people, "Either you join the church or you can't defend yourself on this point." And that it seems to me is not either the wise or sensible or I would say even the true way.

Part of the reasons we have rights language, there is a much older tradition in the West, but certain schisms in that tradition led the Thirty Years' War, in which people bloodied one another over who had the better account of the immortality of the soul.

DR. PELLEGRINO: Thank you.

We have time for one or two more comments. Janet?

DR. ROWLEY: Well, I generally sit these discussions out because I feel so ill-prepared and then so shallow in any kind of comments that I might make or so. "Untutored," I suppose, is a better word.

And following up on what Leon just said, I have always been impressed with what I consider the violations of human dignity that are committed in the name of religion. So, you know, I think that religion, Christian, Muslim, Buddhist, whatever, has a lot to answer for in terms of violations of human dignity.

I think also that this Council has done — I'm not sure whether we have done some damage to what I would consider human dignity. And I come back, and it's really too bad that Mike isn't here because I think his book The Ethical Brain and the discussion of ethics or altruism, as I can recall, — and it's a while since I read the book — being somewhat near to some of the aspects toward the end that Peter was getting at, that we really found as a society that we're a lot better if we behaved ethically and morally toward one another, however that is defined, than if we don't.

And the things that Floyd was talking about as to understanding where in the brain some of these impulses might actually be located makes it, if you will, a scientific, rather than a philosophical or a religious, question.

And so I'm concerned that we have often overridden reason and freedom in the name of dignity and said that my reason and freedom are defective or you have a right as an individual based on what you think human dignity requires to overrule what I might think because you're more right and my reason leads me in the wrong direction.

And I think that there is a certain hubris in your saying that your view of dignity requires certain action and my view of dignity leads to trampling some of these. Your view of dignity can't trample my rights, my reason, my freedom, my autonomy because you're right and I'm wrong. And I think that this is a real concern that this view can in itself lead to a trampling of human dignity.

DR. PELLEGRINO: Thank you very much, Janet.

Just one more. Paul?

DR. MCHUGH: Well, I, like Janet, often find myself overwhelmed by my ignorance in these areas, but I do think that it's important to say some things from that interesting interface between science

and art, namely medicine and its practice and what it means.

I'm going to turn back, actually, to Dr. Rowley in a minute to make my point. And that point comes in a number of different ways. But one of the things that I found great about our Council which has happened over this time has been this combination of our interest in what is basic and then what is expressed.

It's unique, I think, in Council work, that we both talked about the science and then published this book on what fundamentally were the expressions of the poets.

Our Council has worked in both of those arenas remarkably effectively and had very interesting conversations. Leon's recent article on this speaks to that as he talks about the distinctions that he wants to draw between human beings and being human and then ingeniously brings them together in this wonderful circle of the circle of being, as it were and, therefore, evokes for me that wonderful phrase from a great poet, the Irish poet, William Butler Yeats, in that poem "Among the Schoolchildren," where he ends up with saying, "How do we know the dancer from the dance?" And that speaks to what the dignity really is.

We hear about the material, and then we hear about what happens. We don't find inspiration of Cal Ripken in the orthopedic clinic. We find it on the field. But we can help him if he gets into trouble.

Now, I want to come back to this issue that Professor Meilaender wants to dismiss, namely this image and likeness of God, because, in point of fact, I find that both as an Augustinian and as a contemporary person, a very important issue for us and for me.

I want to come back to Janet in this way because, first of all, Janet, although I agree with you that in religion we have caused lots of trouble, I wish it were only religious people that had caused a lot of trouble.

The real problems we get are what we believe. Okay? And in the Twentieth Century, did we stop believing in God and we caused 100 million deaths? And we couldn't come close to that when we believed in God. So it's what we believe and how we use our belief.

Now, I just want to tell you what I believe about what gives human beings their dignity because it's in their image and likeness to God. And where do I get that? How do I find it? I find it in the Trinitarian conception of God. I guess that's Christian. I guess it's Christian.

(Laughter.)

DR. MCHUGH: And how do I see it expressed, especially expressed, on a day I spent in a lecture hall at Hopkins listening to Janet? Janet came and talked about her work and showed us what came of it and inspired our lecturer this morning.

The Trinitarian idea is that there are three things about human beings and three things that are in God. One is the capacity, the executive capacity, for conceiving of something, conceiving something could be the father, if you will; the work of working it through and articulating one thing after another, the word, the Son, if you would; and, finally, the inspiration given to others and inspiring us by seeing it. All of these were done by Janet.

(Laughter.)

DR. MCHUGH: She conceived of this problem of the leukemia of these children. She worked not just from finding the chromosome but then worked out the molecular details. And it was a hell of a lot of work. And she showed us all the various people that had contributed to it.

But then at the end, we realized together what this journey meant for us, what it did in dignity to give us cures for these children but not simply that practical and, as our friend showed us today, the loss of death, but simply the sense that this experience, this expression of a human being in action, you know, for me, it just filled my heart and filled the room in my opinion with everything.

So I am interested in expressing what I mean by human dignity in this Trinitarian expression, where we can see it, where we can see it in action, where we can — I don't want to say worship it at this level but certainly celebrate it. I mean, I celebrated that day. And I still remember it, of course. And I could tell the dancer from the dance.

And it's in that arena that our Council has spoken about dignity in action. Leon speaks about it today. We have heard about it from Gil and everything. And I come down to thinking it's Christian.

DR. PELLEGRINO: Thank you very much, Paul.

Let me again say to Council members I hope relative to this discussion and looking at the papers, that you will be inspired to write your own comments. I know that Adam Schulman will welcome them.

Indeed, Adam, would you like to say a word or two about where the volume is? And I think that that will bring us to the conclusion of our meeting.

DR. SCHULMAN: Yes. I would just like to reiterate what Dr. Pellegrino said, that we still would welcome any submissions you would like to give in the form of comments to the essays that you have received.

We haven't received too many to date, but I do think that as the volume gets closer to completion and publication, it will be a much stronger and much more interesting product if it's not just a stand-alone collection of essays but includes as well your considered reactions and comments on these papers. I think it will be a much more interesting thing for the public to read when it shows what the Council members made of these essays.

So as we are working on editing these essays and we're really fairly flexible about when you can submit these things; that is to say, even until fairly late in the editing process, there would be room for member comments on these essays.

So I encourage you if you haven't done so to think over the essays that you have ready. And if there is one that particularly interests you, we would be delighted to receive commentary on it.

DR. PELLEGRINO: Thank you very much, Adam. Thank you for undertaking the task of putting the papers together into an anthology.

SESSION 7: PUBLIC COMMENTS

DR. PELLEGRINO: Let the record show that no one has signed up for public comments. And, therefore, we will not have the section on comments from those in the audience. No one has requested.

Thank you all very much for attendance at the meeting. And thank you for your participation.

(Whereupon, the foregoing matter was concluded at 12:05 p.m.)

Edmund D. Pellegrino, M.D.

Council chairman

Dr. Pellegrino is Professor Emeritus of Medicine and Medical Ethics and Adjunct Professor of Philosophy at Georgetown University.

He has served as Director of the Center for Clinical Bioethics at Georgetown University; head of the Kennedy Institute of Ethics and director of the Center for the Advanced Study of Ethics at Georgetown; President of Catholic University; President and Chairman of the Yale-New Haven Medical Center; Chancellor and Vice President of Health Affairs at the University of Tennessee; founding Chairman of the Department of Medicine at the University of Kentucky; and Founding Director and Vice President of the Health Sciences Center, State University of New York, Stony Brook, where he oversaw six schools of health sciences and the hospital, and served as Health Affairs Dean of the School of Medicine.

He has authored or co-authored 24 books and more than 550 published articles; is founding editor of the *Journal of Medicine and Philosophy*; a Master of the American College of Physicians; Fellow of the American Association for the Advancement of Science; member of the Institute of Medicine of the National Academy of Sciences; recipient of a number of honorary doctorates; and a recipient of the Benjamin Rush Award from the American Medical Association, and the Abraham Flexner Award of the Association of American Medical Colleges.

In 2004, Pellegrino was named to the International Bioethics Committee of the United Nations Education, Scientific and Cultural Organization (UNESCO), which is the only advisory body within the United Nations system to engage in reflection on the ethical implications of advances in life sciences.

Throughout his career, Dr. Pellegrino has continued seeing patients in clinical consults, teaching medical students, interns and residents, and doing research. Since his retirement in 2000, Dr. Pellegrino has remained at Georgetown, continuing to write, teach medicine and bioethics, and participate in regular clinical attending services.

<< Return to Council Member List :: next >>

Floyd E. Bloom, M.D.

Council Member

Floyd E. Bloom was until March 2005, Chairman of the Department of Neuropharmacology at the Scripps Research Institute. He is currently professor emeritus in the Molecular and Integrative Neuroscience Department at TSRI, and the founding CEO and board chairman of Neurome, Inc. He previously was Director of Behavioral Neurobiology at the Salk Institute and Chief of the Laboratory of Neuropharmacology of NIMH.

He has received numerous awards, including the Pasarow Award in Neuropsychiatry and the Hermann van Helmholtz Award, the Sarnat Award for Mental Health Research, as well as a number of honorary degrees from major universities. He was the editor-in-chief of *Science* magazine from 1995 to 2000.

Dr. Bloom was born in Minneapolis, Minn., in 1936. He attended Southern Methodist University in Dallas, Texas, where he received an AB degree cum laude and then an MD degree, cum laude from Washington University in St. Louis, Mo.

He is a member of the National Academy of Science (1977), The Institute of Medicine (1982), The American Philosophical Society (1989) and the Royal Swedish Academy of Science (1989).

Dr. Bloom has authored or co-authored a total of 32 books and monographs, 415 original research articles, 256 solicited articles and reviews, 59 editorials, and more than 300 abstracts.

<< previous :: Return to Council Member List :: next >>

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Rebecca Dresser, J.D., M.S.

Council Member

Rebecca Dresser, J.D., M.S. Daniel Noyes Kirby Professor of Law, Washington University School of Law, and Professor of Ethics in Medicine, Washington University School of Medicine. Professor Dresser has written extensively on bioethical issues, and she serves on the editorial board of IRB: Ethics and Human Research. Her book, *When Science Offers Salvation: Patient Advocacy and Research Ethics*, was published in 2001. She is also a co-author of *The Human Use of Animals: Case Studies in Ethical Choice* (1998) and *Law and Bioethics: Cases, Materials and Problems* (2003).

<< previous :: Return to Council Member List :: next >>

Nicholas N. Eberstadt, Ph.D.

Council Member

Nicholas Eberstadt is the Henry Wendt Chair in Political Economy and Government at the American Enterprise Institute in Washington DC. He is also Senior Adviser to the National Bureau of Asian Research, and for many years was a member of the Harvard University Center for Population and Development Studies.

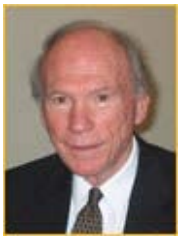
His areas of inquiry include demography, economic development and international security. He has served, inter alia, on the Board of Scientific Counselors for the US National Center for Health Statistics, the Visiting Committee for the Harvard School of Public Health, and the Global Leadership Council of the World Economic Forum.

His many books include *Poverty In China*, *Fertility Decline in the Less Developed Countries*, *The Tyranny of Numbers*, *Prosperous Paupers and Other Population Problems* and *The Poverty of "The Poverty Rate": Measure and Mismeasure of Want in Modern America*.

<< previous :: Return to Council Member List :: next >>

Daniel Foster, M.D.

Council Member



Daniel Foster, M.D. John Denis McGarry, Ph.D. Distinguished Chair in Diabetes and Metabolic Research, University of Texas Southwestern Medical School. Dr. Foster, whose research is in intermediary metabolism, has received the Banting Medal, the Joslin Medal, the Tinsley R. Harrison Medal and the Robert H. Williams Distinguished Chair of Medicine Award for his work. He is a member of the Institute of Medicine of the National Academy of Sciences and is a Fellow of the American Academy of Arts and Sciences. He was chairman of the Department of Internal Medicine at UT Southwestern for 16 years.

<< previous :: Return to Council Member List :: next >>

Michael S. Gazzaniga, Ph.D.

Council Member

Michael Gazzaniga, Ph.D., is the outgoing David T. McLaughlin Distinguished University Professor in Cognitive Neuroscience and Director of the Center for Cognitive Neuroscience at Dartmouth College and the incoming Director of Sage Center for the Study of Mind at the University of California, Santa Barbara. Dr. Gazzaniga conducts research on how the brain enables the mind. He is a fellow of the American Neurological Association, as well as the president of the American Psychological Society and a member of the American Academy of Arts and Sciences and the Institute of Medicine. His publications include *Cognitive Neurosciences III* (2004), *The New Cognitive Neurosciences* (2000) and *The Mind's Past* (1998). His new book, *The Ethical Brain*, was published in 2005.

<< previous :: Return to Council Member List :: next >>

Robert P. George, J.D, D.Phil.

Council Member

Robert P. George is McCormick Professor of Jurisprudence and Director of the James Madison Program in American Ideals and Institutions at Princeton University.

He is the author of *Making Men Moral: Civil Liberties and Public Morality* (1993) and *In Defense of Natural Law* (1999), and editor of *Natural Law Theory: Contemporary Essays* (1992), *The Autonomy of Law: Essays on Legal Positivism* (1996), and *Natural Law, Liberalism, and Morality* (1996), all published by Oxford University Press. He is also editor of *Great Cases in Constitutional Law* (2000) and co-editor of *Constitutional Politics: Essays on Constitution Making, Maintenance, and Change* (2001), from Princeton University Press, and *The Clash of Orthodoxies* (2002), published by ISI Books. He is co-author of *Embryo: A Defense of Human Life* (2008, Doubleday) and *Body-Self Dualism in Contemporary Ethics and Politics* (2008, Cambridge University Press).

In 2008, Professor George received the Presidential Citizens Medal at a ceremony in the Oval Office of the White House. He is a winner the Bradley Prize for Intellectual and Civic Achievement; the Sidney Hook Memorial Award of the National Association of Scholars; and the Philip Merrill Award for Outstanding Contributions to the Liberal Arts of the American Council of Trustees and Alumni.

A graduate of Swarthmore College and Harvard Law School, Professor George earned a doctorate in philosophy of law from Oxford University. He was elected to Phi Beta Kappa at Swarthmore, and received a Knox Fellowship from Harvard for graduate study in law and philosophy at Oxford. He holds honorary doctorates of law, letters, science, ethics, civil law, humane letters, and juridical science.

Professor George is a member of UNESCO's World Commission on the Ethics of Scientific Knowledge and Technology. From 1993-98, he served as a presidential appointee to the United States Commission on Civil Rights. He is also a former Judicial Fellow at the Supreme Court of the United States, where he received the 1990 Justice Tom C. Clark Award. He is the recipient of a Silver Gavel Award of the American Bar Association, the Paul Bator Award of the Federalist Society for Law and Public Policy. In 2007 he gave the John Dewey Lecture in Philosophy of Law at Harvard. In 2008 he gave the Judge Guido Calabresi Lecture at Yale and the Sir Malcolm Knox Lecture at the University of St. Andrews in Scotland.

Professor George is a member of the Council on Foreign Relations, and serves as Of Counsel to the law firm of Robinson & McElwee.

<< previous :: Return to Council Member List :: next >>

Alfonso Gómez-Lobo, Dr. phil.

Council Member

Alfonso Gómez-Lobo, Dr. phil. Ryan Family Professor of Metaphysics and Moral Philosophy, Georgetown University. Professor Gómez-Lobo specializes in Greek philosophy, Greek historiography, the history of ethics, and contemporary natural law theory. He is the recipient of several awards, including a research fellowship from the Guggenheim Foundation. His latest book, *Morality and the Human Goods*, was published by Georgetown University Press in 2002.

<< previous :: Return to Council Member List :: next >>

William B. Hurlbut, M.D.

Council Member

William B. Hurlbut, M.D. Consulting Professor, Deparatment of Neurology and Neurological Sciences, Stanford Medical Center, Stanford University. Dr. Hurlbut's main areas of interest involve the ethical issues associated with advancing biotechnology and neuroscience, the evolutionary origins of spiritual and moral awareness, and the integration of philosophy of biology with theology. He has worked with the Center for International Security and Cooperation on a project formulating policy on Chemical and Biological Warfare and with NASA on projects in astrobiology. He is the author of "Altered Nuclear Transfer," a technological proposal to our nation's impasse over stem cell research.

<< previous :: Return to Council Member List :: next >>

Leon R. Kass, M.D., Ph.D

Council Member

Leon R. Kass, M.D., Ph.D., is the Addie Clark Harding Professor in the Committee on Social Thought and the College at the University of Chicago and Hertog Fellow in Social Thought at the American Enterprise Institute. He was chairman of the President's Council on Bioethics from 2001 to 2005.

A native of Chicago, Dr. Kass was educated at the University of Chicago where he earned his B.S. and M.D. degrees (1958; 1962) and at Harvard where he took a Ph.D. in biochemistry (1967). Afterwards, he did research in molecular biology at the National Institutes of Health, while serving in the United States Public Health Service.

Shifting directions from doing science to thinking about its human meaning, he has been engaged for more than 30 years with ethical and philosophical issues raised by biomedical advance, and, more recently, with broader moral and cultural issues. From 1970-72, Dr. Kass served as Executive Secretary of the Committee on the Life Sciences and Social Policy of the National Research Council/National Academy of Sciences, whose report, *Assessing Biomedical Technologies*, provided one of the first overviews of the emerging moral and social questions posed by biomedical advance.

He taught at St. John's College, Annapolis, MD, and served as Joseph P. Kennedy, Sr., Research Professor in Bioethics at the Kennedy Institute of Ethics at Georgetown University, before returning in 1976 to the University of Chicago, where he has been an award-winning teacher deeply involved in undergraduate education and committed to the study of classic texts.

His numerous articles and books include: *Toward a More Natural Science: Biology and Human Affairs* (1984); *The Hungry Soul: Eating and the Perfecting of Our Nature* (1994); *The Ethics of Human Cloning* (1998, with James Q. Wilson); *Wing to Wing, Oar to Oar: Readings on Courting and Marrying* (2000, with Amy A. Kass); *Life, Liberty, and the Defense of Dignity: The Challenge for Bioethics* (2002); and *The Beginning of Wisdom: Reading Genesis* (2003).

His widely reprinted essays in biomedical ethics have dealt with issues raised by in vitro fertilization, cloning, genetic screening and genetic technology, organ transplantation, aging research, euthanasia and assisted suicide, and the moral nature of the medical profession.

Dr. Kass is married to Amy Apfel Kass, Senior Lecturer in the Humanities at the University of Chicago and Senior Fellow at the Hudson Institute. The Kasses have two married daughters and four young granddaughters.

Return to Council Member List :: next >>

Peter A. Lawler, Ph.D.

Council Member

Peter Augustine Lawler is Dana Professor and Chair of the Department of Government and International Studies at Berry College. He teaches courses in political philosophy and American politics and has won several awards from Berry for doing so.

He is executive editor of the acclaimed quarterly journal, *Perspectives on Political Science,* and has been chair of the politics and literature section of the American Political Science Association. He also serves on the editorial board of the new bilingual critical edition of Alexis de Tocqueville's *Democracy in America* and on the editorial boards of several journals. He is a member of the Society of Scholars at the Madison Center at Princeton University, the George Washington Professor on the American founding for the Society of Cincinnati for the state of Georgia, and he is a member of President Bush's Council on Bioethics.

He has written or edited ten books. His newest book, *Aliens in America: The Strange Truth about Our Souls* is a starred, featured selection in *Booklist*, the journal of the American Library Association. Another recent book, *Postmodernism Rightly Understood,* was also widely reviewed and praised. His very long introduction to a new edition of Orestes Brownson's *The American Republic* is now available.

His *American Political Rhetoric* (edited with Robert Schaefer) is used in introductory American government courses at a sizeable number of colleges and universities. The fifth edition was just published.

Lawler has published more than 125 scholarly articles, chapters, and reviews. His writings have appeared in such scholarly journals as the *Review of Politics, Government and Opposition, The South Atlantic Quarterly, The International Philosophical Quarterly, American Political Science Review, Journal of Politics, Gravitas, Interpretation: A Journal of Political Philosophy, Polity, Modern Age, Public Integrity, The Intercollegiate Review, Presidential Studies Quarterly, The Public Interest, Perspectives on Political Science, First Things, The Good Society, The New Atlantis, and Society*. He is also published in more popular magazines such as *The Weekly Standard, Current, The Claremont Review of Books, The University Bookman, The American Enterprise, Crisis, The National Review*, and *National Review Online.*

Some of the topics of his recent articles and chapters include Shakespeare's *The Tempest*, William Alexander Percy, Walker Percy, Alexis de Tocqueville, biotechnology, bourgeois bohemian virtue, religion and conservatism, compassionate conservatism, conservationism, the filmmaker Whit Stillman on nature and grace, disco and democracy, *Casablanca* and the American dream, the future of human nature, the utopian eugenics of our time, the rise and fall of sociobiology, Richard Rorty, grade inflation and the Ivy League, Harvey Mansfield and Carey McWilliams, caregiving and the American individual, Christopher Lasch, virtue voters, culture wars, Flannery O'Connor and nihilism, Orestes Brownson, and postmodernism rightly understood.

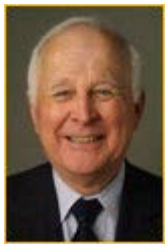
Lawler has given invited lectures at more than 50 colleges and universities. He has received a large number of grants from both the Liberty Fund and the Earhart Foundation, as well as numerous other foundations.

Dr. Lawler recently edited a book on Tocqueville and American political life today and the fifth edition of *American Political Rhetoric*. He wrote an introduction to the new Sheed and Ward edition of John Courtney Murray's *We Hold These Truths*, and book chapters on religion and the American founding, Locke and American greatness, Flannery O'Connor, and *Casablanca*.


THE WHITE HOUSE

Paul McHugh, M.D.

Council Member



Paul R. McHugh, M.D. is the University Distinguished Service Professor of Psychiatry at the Johns Hopkins University School of Medicine. He was the Henry Phipps Professor of Psychiatry, Director of the Department of Psychiatry and Behavioral Sciences at the Johns Hopkins University School of Medicine, and psychiatrist-in-chief at the Johns Hopkins Hospital from 1975-2001. He is the author of 4 books and more than 150 papers.

<< previous :: Return to Council Member List :: next >>

The President's Council on Bioethics

Home Site Map Disclaimers Privacy Notice Accessibility NBAC HHS

Gilbert Meilaender, Ph.D.

Council Member

Gilbert Meilaender, Ph.D. Richard & Phyllis Duesenberg Professor of Christian Ethics at Valparaiso University. Professor Meilaender is an associate editor for the *Journal of Religious Ethics*. He has taken a special interest in bioethics and is a Fellow of the Hastings Center. His books include *Bioethics: A Primer for Christians* (1996, 2005), *Body, Soul, and Bioethics* (1995). He has recently edited (together with William Werpehowski) *The Oxford Handbook of Theological Ethics.*

<< previous :: Return to Council Member List :: next >>

JANET D. ROWLEY, M.D., D.SC.

COUNCIL MEMBER

Janet D. Rowley, M.D., D.Sc. Blum-Riese Distinguished Service Professor of Medicine, Molecular Genetics and Cell Biology, and Human Genetics, Pritzker School of Medicine, University of Chicago. Dr. Rowley is internationally renowned for her studies of chromosome abnormalities in human leukemia and lymphoma. She is the recipient of the National Medal of Science (1999) and the Albert Lasker Clinical Medicine Research Prize (1998), the most distinguished American honor for clinical medical research.

<< previous :: Return to Council Member List :: next >>

The President's Council on Bioethics

Home Site Map Disclaimers Privacy Notice Accessibility NBAC HHS

Diana J. Schaub, Ph.D.

Council Member

Diana J. Schaub is a professor and chairwoman of the department of political science at Loyola College in Maryland. From 1994 to 1995 she was the postdoctoral fellow of the Program on Constitutional Government at Harvard University. In 2001, she was the recipient of the Richard M. Weaver Prize for Scholarly Letters. Ms. Schaub has taught at the University of Michigan at Dearborn and served as assistant editor of the National Interest. She has her A.B. from Kenyon College, where she was elected to Phi Beta Kappa, and an M.A. and Ph.D. from the University of Chicago. She is the author of *Erotic Liberalism: Women and Revolution in Montesquieu's "Persian Letters"* (1995), along with a number of book chapters and articles in the fields of political philosophy and American political thought. Ms. Schaub's work also appears in the *New Criterion*, the *Public Interest*, and *The American Enterprise.*

<< previous :: Return to Council Member List :: next >>