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Genetics Subcommittee

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P R O C E E D I N G S

[3:10 p.m.]

DR. MURRAY: Let's call the meeting to order.

I am going to try to do two things this afternoon and one is to hear from and speak with Bartha Knoppers, who has looked at positions around the world on issues concerned with tissue samples, human tissue samples.

Then we are going to hear from Dr. Elisa Eiseman about what actually -- what are the realities of tissue sampling in the world.

So, Bartha, would you -- of course, I know you well, but would you introduce yourself to the --

Agenda Item: Genetic Tissue Storage: International Comparative Positions

DR. KNOPPERS: I am a professor of comparative medical laws, as well as genetics ethics and law, children and the law, et cetera, at the University of Montreal. My field is research. In the last 15 years or so, it has been in the area of new technologies, be they reproductive, genetic, biotech and so on.

I head up a research team on biotechnology law and society and I attempt to keep track of what is happening around the world, but not everywhere, believe me. So, maybe -- do you want any further introduction? I chair the UGAL(?), UGAL International Ethics Committee from the Human Genome Organization. And I also sit on the UNESCO Ethics Committee, the one that is attempting to draft the universal declaration on the protection of the human genome and human rights.

And I think maybe Noelle Lenoir, who is the chair of that committee, might be popping in later during this particular session.

DR. MURRAY: We have a paper from you, a draft paper, which some of us received yesterday, and had a chance to read. Not everyone did. So, if you could give briefly in 10 or 15 minutes a description of what you set out to do and the highlights of your findings and then the rest of the time, I would like to just have some conversation.

DR. KNOPPERS: All right. This paper is very much in draft. Please, do not cite it in any way for the time being, a typical lawyer's statement, but that is -- to my fellow authors, I told them I would tell you that. So, I am.

I found several errors -- we changed all the

footnote numbers. As you notice, we are covering about 80 different reports at the same time and as things come in, we have to change everything and I am not very good in informatics. So, I haven't quite learned how to do this yet. There are no glaring errors.

I will, however, in about two weeks send a revised copy. I also was very careful not to be too conclusive, i.e., not -- I did draw some conclusions, but I have about another four or five pages germinating, simply because this report is being presented not only to you, but also to the UGAL Ethics Committee and part of it was funded UNESCO and I would prefer that every agency take care of their own conclusions and not be leading in any respect.

But when I submit it for publication in England, which is where it will be eventually in a book, I will be much more personal. There are already some personal conclusions. You will see it on the last page and I will get to that in a minute.

Okay. What is the methodology used in preparing this particular report? Oh, by the way, I have to do a piece of advertising. There is a book that has just come out on human DNA law and policy, which is the report of a conference I chaired last year, the First International Conference on Human DNA Sampling.

Okay. The methodology used is one that we have developed at the research center where I work in the last number of years, is that we look not at the literature, though, obviously, we read all that stuff, but we take as a basis for our report all official, obviously, all laws, in quotes, that exist on a given topic at the international, regional or national level, that we received that are official, i.e., we do not deal with bills.

So, you will find the United States described rather succinctly and certainly not covering these kinds of bills that come and go and live and have different lives and so on. Sorry for that. All right. So, we take laws. We take reports that come from government-appointed national ethics committees or standing committees or commissions of inquiry or health councils or -- at the next level.

And we also deal -- I should say cover professional societies that have come out with statements that are published. If we find something that is unpublished, we might use it, but we will indicate that it is unpublished. We really want to make sure that we have got, you know, the official version.

Then we, depending on the theme, we work by the

international, regional and national level. We try to regroup by subtheme, but if you read this paper, you will notice that when we came to the issue of retrospective versus prospective use of archive tissues, we did the United States all by itself because there are at a minimum ten conflicting statements dealing with what you can or cannot do. And I will get to that in a minute. Because we usually do one line and try to put three or four countries that have the same position in one line. Otherwise, it gets too boring. But when a country is so different, we will put it apart. So, that is a little bit about methodology.

I also forgot to put our definition of what DNA is, but I presume you all know. It will come in on the final paper.

This paper has four parts. It sort of sounds like a Latin book. The first is the status of human genetic material. The second is the issues of consent and choice, the third of confidentiality and access and the fourth, which is rather succinct, on security mechanisms simply because it is not something that really turns me on. But we have to cover it because I finally came to realize after having worked in repro tech for quite awhile that it is in quality assurance that the beginning of respect for ethical principles really starts.

On the issue of status, this is an endless debate ongoing and will go on forever as to whether tissue cells, blood, leftovers, however you want to describe it, are part of the person and in what in European and most civil law systems would be called a personality right, not that it is you but it is an attribute or an extension of you. I take for granted that nobody presumes DNA is a person. So, you know, that is an attribute of your personality rights or is it something that you could have control over in terms of owning it and, thus, alienating it, as we would say in civil law, to make profit.

So, there is a possibility of individual commercialization. I quote Blackstone on page 2, who says that these rights -- this is the traditional division between personality rights and property rights.

While we were engaging this and we have been engaging it for about ten years or so, this debate, things are happening. So, I am going to be very short on the status issue because it really is ultimately, unfortunately, because of the commercialization generally around the world of genetic research and genetic technologies, going to be more symbolic than real.

The only place it really kicks in, pardon the expression, is whether you yourself can ever profit from your tissues, when they are, you know, genetically interesting or unique or whatever or as a collectivity, you sign away access to your community for possible percentage of royalties or patent rights or whatever in the future. That is where a property approach would allow you to do that.

A personality approach says "no," it doesn't mean you can't be indemnified if you spend two days traveling or whatever, but you cannot get paid for participating or giving your tissues. They are an extra patrimonial, as we say.

Most European countries take this position. You will also note that UNESCO and the European Convention have said that the human body and its parts and the human genome in its natural state, natural state, cannot give rise to financial gain. So, broadly, body parts as such and human genome in its natural state as such cannot give rise to financial gain. This is to underscore non-commercialization, which is a very important philosophical concept in most countries.

This does not mean you can't have intellectual property. This does not mean you cannot patent. It simply says that the beginning stage you do not own in an economic sense your body or your body parts.

Now, the only country that

DR. MIIKE: That is not really true in terms of property law in the sense that bodies used to be considered property by relatives after they died.

DR. KNOPPERS: A quasi property right after death. Relatives have a quasi property right after death to dispose of the body either according to the will of the person under a will, a written will, or because the law grants them certain rights to incinerate, to bury, to donate to science and so on.

DR. MIIKE: But from your standpoint, that has no relevance to this issue?

DR. KNOPPERS: No. A quasi property right is an exception, if you like, because your personality no longer exists. It dies with you.

DR. MIIKE: But that was discussed in the early organ --

DR. KNOPPERS: Yes, it was. Oh, yes. In organs, in grave robbing, in sperm donation. I mean, there are many -- I am not going to get into the status too long because we

are going to stay there, but you are right. There are --

DR. MURRAY: There is a wonderful discussion and it may, in fact, be in Blackstone about this curious -- no, it is not Blackstone. It is in the Keaton on torts, I think -- this famous series of cases where a scholar writing about it reflected that it is a curious kind of property right because it can only lead to sort of liabilities on your part. You are liable to make sure this body is disposed of in some honorable way, in some way in keeping with the will of the --

DR. MIIKE: What about some of the commentaries -- some other jurisdiction would reverse that and give a property right?

DR. KNOPPERS: Might do so. I was just saying the only country that to date has an official policy position that they are -- well, a country doesn't, there is a Genetic Privacy Act, which as you know does grant a property right to -- let me just find the exact quote --

DR. MIIKE: I haven't had the time to read your paper, so if it is in here, then just tell me to shut up.

DR. KNOPPERS: Yes, it is.

No, no, no, I won't ever do that, no. No, no. It is recognized.

What is interesting about the Genetic Privacy Act is in the states that have adopted it, one of the first things that they take out is that because no researcher can get grants -- I am off the topic a little bit, but it is important, I think -- will get grants from a venture capital fund or from a biotech firm or company or whatever if that issue hasn't been cleared up because even though it is probably fictitious that one day you are going to get 37 cents, ten years later because they found some, you know, product -- you know, like in the Moore(?) case. The Moore and Hadihai(?) and the Hawaiian and so, those are exceptional cases. None of us are really that interesting.

It is true there are exceptionally, in quotes -- how do I put it -- genetically rich, pardon the pun, individuals, but the more case -- if the Genetic Privacy Act gains hold or the philosophy there, it might be revisited, but I know in New Jersey and so on, it has taken that property line out.

What is interesting about the status is that ultimately, I think, and this is personal, that the human body, organs, tissues, to me, should not be either property or person. It should have a -- what we call "la sui" generis status, a unique status. The intellectual property

and so on is one of those sui generis categories where we should look. We can't figure this out.

We all agree that we have to exercise control. We have to have choices. We have to have consent. Even if we can agree to disagree on the purposes of that or I should say the origins of that, pardon, let's recognize it as being different, give it a sui generis status and develop rules to respect the inherent dignity of the person.

DR. MIIKE: -- in its natural state.

DR. KNOPPERS: Even in its natural state.

DR. MIIKE: No, no, no. I thought you were limiting that to in its natural state.

DR. MURRAY: To only in its natural state.

DR. KNOPPERS: But it is sui generis only in its natural state, yes.

Which brings me to the second part, which is on consent and choice, which is ultimately where the true issues lie in property or person, you will find out that looking at the kind of choices that are offered under either approach are pretty well the same, the kinds of controls that are suggested or choices offered to participants.

The only difference is under a property approach, you can offer as the Genetic Privacy Act does a certain control over commercial benefits, transfer to other commercial banks, possible returns and so on. So, that is the only difference under the property approach from the person approach.

Under the consent and choice part of my paper, you will note an increasing -- I think we have reached as far as we can go on the number of choices that we can fit in on consent forms. In the sense that there is now sort of a core elements list, which I think is as far as we can go in respecting individual choices made on the basis of spiritual and personal values, which luckily in a multi-cultural society are still there and are still very -- in a pluralistic society and multi-cultural society are still present.

These include, as you know, whether you wish to be told of the results or not, whether you want to know about incidental findings, whether you want to be contacted in the future, would you like your samples to be used for other research, under the property approach, your interest in potential commercial products or whatever and under the property approach, also the possibility of withdrawing not from the project, which, of course, is in all research. You can always withdraw your consent to participate in research,

but actually withdrawing your sample.

Don't ask me how that works because it doesn't, but it is there as an option that is offered. We have increasingly a standard list of core elements that are appearing. What we are missing and you will see that in the five pages covering the American positions, which range from extreme -- what I would call individualized automistic approach, my body, myself, my DNA, me. Even after death, you know, nobody can touch it because it is -- the earlier, that kind of approach to a very liberal approach coming from the American society's pathology, for instance, who in reaction to this individualized automistic approach said, oh, I am now a general consent. This has gone way too far. We have gone haywire, you know, with consent and so on.

Somewhere in between, particularly in the last year, 1997, you will see positions that recognize the social validity and benefits of consent. I mean, we do live in society and, yet, respect individual difference and individual values. We are seeing a move back from, let's say, 1995, when we had some positions that would literally stop all epidemiological and all kinds of research because the dead people didn't say what they wanted before they died and, so, you know, couldn't touch it. After all, it was them.

I don't mean to be facetious, but I am describing it in a way that sort of brings the issues in.

DR. MURRAY: Bartha, this is on page 9 of the paper in the first full paragraph. You refer to two countries, France and Denmark, that have various kinds of national registries. Biological banks, you call them or bio banks. Would any repository of human tissue, including a pathology laboratory that kept samples, would that be included, do you know, in these registries?

DR. KNOPPERS: The ordinance, as they call it in France, on what constitutes a bank, I did not include in -- at least I don't think so. I will have to check under -- there is only one that I have received so far. I mean, I follow it in the French, but I don't -- no.

For each one of these bioethics laws, there are then what they call decrees, which are about 300 pages of details on -- it is like your Federal Registry. At first glance, knowing the French, I would say "yes," but I would definitely want to check it out to make sure that --

DR. MURRAY: I guess even more of interest to me right now is is there sufficient experience with these national registries to have any idea whether they do any

good or whether they have been an impediment or --

DR. KNOPPERS: Do you have tumor registries here in the United States? Well, there is an example to see if they work and can work in law, I guess. That, I know. I know about the tumor registries and how they work. Whether these Danish bio bank, which I think dates to what your --

DR. EMANUEL: DR. MURRAY: But they don't keep samples. Tumor registries don't keep samples.

DR. KNOPPERS: They are not repositories --

DR. EMANUEL: They are more epidemiological than --

DR. KNOPPERS: They are record repositories.

DR. EMANUEL: -- than pathological sample collectors.

DR. MIIKE: The way this thing is phrased, it seems to me that if you have some pathological tissues, you only register with them if you then start to use them in a particular study.

DR. KNOPPERS: Then you become a bio bank. Because every pathology lab or every hospital in France would have to sign up if that were the -- which sentence or which footnote are you talking about, Tom.

DR. MURRAY: Well, I am actually reading a 1996 ordinance language. It says, "Or use to the same end samples already taken of derivatives thereof." So, it seems to me that it is not simply that in a normal course of a hospitalization that all of those have to be registered, but only if you subsequent --

DR. KNOPPERS: For the purposes of research. Thanks.

So, Tom, I am not going to describe those four pages of the conflicting positions here. One interesting European approach under this consent choice is in addition to this wide range of options that you get after your "yes/no" to actual consenting to the research, then is subdivided, is a possibility of being a general consent to use in research, provided it is anonymized or if it is anonymous, obviously, you don't even know it is there, but in the sense that it is an opting out.

For general epidemiological or surveillance studies, simply being informed that this exists and saying "yes" or "no," allows you to opt in or opt out of having your samples, which you are giving, let's say, for Alzheimer's research, used for any other research, provided it is anonymized. Because once it is anonymized, you cannot code it. It is beyond coding. You cannot be found. You

cannot be traced.

There might be some demographic stuff. There might be some clinical stuff, but not enough demographic, clinical data to allow you ever to find the person. So, you enter the realm of not totally anonymous DNA, but you enter the realm of anonymized, which allows you then -- which allows general research to go forward, but would never be of any particular -- there would be no coming back to you. You could never find out and the researcher could never find you no matter where that sample was sent around the world.

DR. MURRAY: I thought I understood the distinction between anonymous and anonymized that you were using. Now I am not sure.

DR. KNOPPERS: Okay. Let's just use the American Society of Human Genetics then -- actually, there are two different -- if you look on page 12, the Canadians, of course, we had to find a different word. We use identifiable, traceable, anonymous, anonymized. But since we are in the United States, we will go to page 15 --

DR. MURRAY: Actually, I like the Canadian definition, but go ahead.

DR. KNOPPERS: Thank you, Tom.

Well, "traceable" simply makes it clearer to people and "identifiable." Anonymous biological materials that were originally collected without identifiers are impossible to link to their sources.

DR. MURRAY: But may have other kinds of information, pathological, clinical information.

DR. KNOPPERS: Might. It might just be strictly debris. It might just be old bloods that have been sitting somewhere with no little things on. You know what people use "anonymous" for mainly? To calibrate machines to.

DR. LO: It is stuff like all PKU samples.

DR. MURRAY: What would you do with material that when it was collected, it was collected, but only with demographic sorts of data?

DR. KNOPPERS: That is anonymized. Anonymized was originally identified and them became anonymized.

DR. MURRAY: I don't wish to embarrass you, but would you mind introducing yourself?

MADAME LENOIR: Well, first of all, I thank you very much, indeed, to welcome me because this is the first time that I have had an opportunity to attend a meeting. I am a jurist by training, but, you know, I have here a colleague and perhaps some others.

I am a member of the French Constitutional Court.

It is my main function, which is not like your Supreme Court, but it is a court, which is involved in the judicial review of the constitution in the French way. So, I am one of the nine judges and one woman. So, I am the token one.

But apart from my main functions, I have international activities and we are colleagues in the same body, which is an advisory committee at an international level and it is the International Committee on Bioethics at UNESCO because you know that long -- the institution of the United Nations, UNESCO is the only one to have a specific competence in science. So, it is promoting research programs and at the same time, has created this committee to which participate very prominent personalities from different countries.

We are 55 from 40 countries and as far as the North America is concerned there is my friend Bartha here and there are two American persons, Bruce Alberts, Sidney Altman and Harold Edgar. So, it is not, I think, a very bad composition and you have people from -- many constitutional judges from supreme courts and jurists, lawyers and scientists and philosophers and diplomats.

This committee was asked by the states of UNESCO to draft a declaration, which is going to be an international instrument. That is to say that it is not similar to a declaration which is made at the end of a congress, for instance. It is not a binding instrument. It is not a treaty, but it is meant to have a moral influence and to try to ensure a certain stability in the field of biotechnology and ethics, which is more and more mediatic(?) -- you say that -- issues for the media with the cloning and all that.

So, I hope very much that no Dolly is -- Dolly is not to have a sister or a brother until November, that is to say, until the adoption of this takes because each time you have a very emotional event in the field of biotechnology. Each time public opinion and politicians ask for prohibitions. So, we don't want that to occur in the next future.

And, secondly, I am always chairing an ethics committee, which has been created at the level of the European Union, but it is a small body. It is an advisory body, which comprises nine members from nine countries of the European Union, and the mission is different because it is a more -- it is directly related to the legislative competence of the European Union. As you know, more and more directive and regulations have to do with biotechnology

and each time the European Union wants to legislate in a field, such as transgenic animals, they ask our advice and we have been asked to say a word about cloning and, of course, we had -- at that time, we made our opinion, the 28th of May. So, your committee was the first one to say something about it. So, we made an opinion that you will have because your president, Mr. Shapiro, has had it.

At present we have been asked to say a word about the research program, which is going to be launched for five years from 1998 to 2002 at the level of the European Union in every field. The research program, which is financed by the European Community and we have been asked to say a word about the ethical issues and legal issues of the research program in the field of biotechnology and biomedicine.

So, bioethics is my dossers(?) -- you say that in English? I am sure that I am going to learn a lot from you.

DR. MURRAY: Well, we are delighted that you could come and to initiate this dialogue.

We are talking about human tissue samples, DNA research. This is the Genetics Subcommittee of the National Bioethics Advisory Commission. The Human Subjects Subcommittee is meeting next door.

This subcommittee has on its agenda also reports on genetic privacy and discrimination and gene patenting, but we haven't begun work on those two easy issues yet.

So, if it is all right with you, we will just continue hearing from Bartha.

DR. KNOPPERS: If it is all right with you, Tom, can we take five more minutes and ask Noelle to say what is happening with the UNESCO declaration. I don't have to leave until 4:30, but maybe it would be nice for the people here around the room to know the relationship between the actual state of the declaration and what is in -- I mean, I did -- my paper does cover -- every section starts with DNF(?) the declaration. So, there is -- but maybe what is happening in November or --

DR. MURRAY: Please.

MADAME LENOIR: Well, the drafting of the declaration was a bit specific because it is an academy body, in fact, the international committee and which was, apart from any pressure of any government, which drafted. The role of Bartha and Edgar was very, very decisive. So, the draft prepared by the committee was submitted to a committee of government and experts, which is a normal diplomatic process because you have two -- when an international organization is drafting an instrument, you

have two stages. The first one is to gather national delegations and your country has a delegation, which is represented by Eric(?) here and he was positive and very helpful because the German had certain very strong position opposed to biotechnology, as you know.

So, this committee had a meeting in July and made a text, which we present the consensus to be more precise. We compromise. It is a consensus but it is, in fact, a compromise. Countries were very much opposed to biotechnology and those were much more in favor, the U.K., the United States, Japan. So, it is a compromise, which represents the balance which has been reached among the states of all nations. Then this text is going to be submitted to the General Assembly of the member states of UNESCO in November 1997.

So, normally, it is going to be adopted by consensus with the possibly reservations from states, but normally it is a final text and I must say that I hope it is a final text because if it is going to be changed, the change will be certainly in favor of prohibitions and we thought that a text of that kind, which is going to be a reference and which must adapt to the change of science and to the change of mentality in the long term, has to have this balanced approach considering -- and this is quite a novelty in the text in that field considering that freedom of research has to do with human rights.

If freedom of research is established in these states as the human rights having to do with the freedom of sorts, which gives another view. Of course, it seems symbolical, but in law we know that symbols can have a parational(?) effect when they are applied in concrete cases.

So, this is the main -- input of the text is the balanced approach. Of course, precise provisions can -- and we have this Article 4, which is very ambiguous, but, in fact, when you examine the different provisions, you can have different comments.

But the main idea is to give a certain stability to this field, to say that, you know, research is an activity, which is considered specifically by the international community at the level of the states and that research has to be protected and fostered and at the same time individual freedom and the concerns of public opinion have to be taken into account, but the balance is very important to change and even to protect politicians when they have to react urgently to the public concern, as was

the case with the cloning recent affair and as is to be the case, perhaps, with another discovery.

So, that is the points. Some articles can be controversial, but I think that on the whole it is the main stream that we tried to -- with great difficulty because, you know, it is a field in which intervene cultures and sometimes even religions. So, it is much more difficult to draft a text of this kind having to do not only with human rights, but also with economy, finance, money and industry.

So, the mixture is a very, very difficult one.

DR. MURRAY: How long has this document been in preparation?

MADAME LENOIR: Well, we have been working during four years, but, in fact, because we consulted hundreds of -- five hundreds or thousands of people, you know. I cannot say that we took into account every remarks because, of course, there is a -- I am struck -- I don't want to be too long, but I am struck by the lack of information of people of the elite of the different nation, which are not involved in science.

I think that they have almost the same level of information -- you know, I made a conference recently before people from different supreme courts, you know, and they don't know about that even if they are very highly educated. They don't know more than -- it is difficult. They don't know more than I do with my Internet, which is a very difficult challenge for me, you know. That is the problem.

DR. MURRAY: If you would be patient and I want to give the opportunity to other members of the commission and the subcommittee if they had any questions about international activities for you.

DR. LO: Let me just ask you, as you presented your recommendations, you had a balance between intellectual freedom, the right to scientific inquiry and I guess the protection of individual subjects of research. As I understand, you placed a very high emphasis on intellectual freedom.

Where does that come from? Is that -- I mean, how did you work out that that was given more weight than the protection of human subjects? In this country, there are a lot of people that feel that the primary thing should be to make sure that no harm is done to people whose tissue is used in this research.

MADAME LENOIR: Well, we say that, of course. The problem of rights is a problem of conciliation, reconcile different values and conflict. But we thought that -- we

said in the text that the human being is primary, of course, and it is not because research and you know that bioethics was born during the Nuremberg trial, more or less, you know.

We say that that the human being is primary and it is not because the research is useful that we can get rid of the right of human beings, their suffering, their agreement, their consent. Of course, the principle is that the human being is to be respected before anything else, but we thought that freedom of thought, you know, is a value, which is similar to any other liberty. That is, you know, in the conciliation, of course, human being is first, but we -- I think that in your legislation, you have freedom of expression and you have also the protection of the -- in privacy. So, when they are in conflict, I think that sometimes privacy -- you know, sometimes privacy is primary vis-a-vis freedom of expression of the press sometimes because you have a private life.

But freedom of expression and privacy are two rights, which are respectfully both. You know, this is the meaning. When there is conflict, of course, you know --

DR. MURRAY: If I heard you correctly, what I understood you to say is that whereas the protection and respect of persons have always been widely recognized as a principle. The notion that scientific research was a form of a kind of free expression or freedom of speech, freedom of inquiry, that hadn't been so formally articulated.

MADAME LENOIR: Well, of course, I don't like to give examples coming from my country, but to give you a concrete example -- I was drafter of the opinion. We made a judgment in 1994 about a legislation, which was about fostering first language in culture. And there was a provision in the law, which states that if a researcher publishes its results, he or she must publish in French, in English, but also in French. Otherwise, there is no public funding. It was to protect the French. So, we say, first of all, freedom of research derives from -- I am sorry to give this example, but, you know -- freedom of research derives from freedom of expression, which is said in the Declaration of Human Rights of 1789, which we applied in now the French Revolution, which says that freedom of explanation is one of the most precious liberty of mankind.

So, we said freedom of research divides from freedom of expression, which is the most precious and we said it is contrary to the freedom of research, which has a constitutional value since 1789 through freedom of -- to limit the grants to the researchers, according to the

language, the use, because it has nothing to do with the scientific quality of the research. It has to do with another purpose, which is the French language.

But now, you know, our minister of education declared one week ago that English is no more a foreign language in France.

So, that is the punch, you know. We say that -- we make the -- and the German did also. They associate freedom with research. I studied the case laws of other countries because you had in certain countries always in conflict, first of all, between religion and research and then between the state and research, you know, and the research community gets more and more autonomous vis-a-vis the other powers and now there is a problem of economy and research and public opinion. It is another challenge, you know.

So, we had to reaffirm the problem, the principle of freedom and research in that context and I think that in the present context of the great tension between the scientific community, industry and public opinion, it is morally appropriate to reaffirm this activity as a free activity. So, that is why we have several articles.

But, of course, it is not because -- you know, freedom is neither general nor absolute. So, it is not because you are free that you can breach other very important values. But in the conflict of values we thought -- and it was approved by the country, I think. They were less prepared to approve other things, but I think that the balanced approach is accepted now.

DR. MURRAY: Thank you.

MADAME LENOIR: There are other problems.

DR. KNOPPERS: Should I continue, Tom?

DR. MURRAY: Yes, please.

DR. KNOPPERS: I am now thinking about the declaration. I have to get my mind back.

Before people entered the room, I had just finished describing the part of the paper on the status of human genetic material. I was finishing up on the consent and choice, which I won't repeat. I simply enumerated the standardized sort of core element that seemed to be appearing after about ten years of discussion in different policy documents around the world.

What I won't describe for lack of time, but in any event it is in the paper are the specific provisions made for newborns, use of newborn samples, where, obviously, the newborns can't speak for themselves, or the use of the

samples from deceased persons, who, obviously, can't speak for themselves.

They are, however, described in the paper and might be of interest to you in terms of the exception, again, made -- and I can underscore this for anonymous studies, surveillance studies or for epidemiological studies.

I stress this point because in the area of genetics, without proper surveillance studies, incident studies or genetic epidemiology studies, hopefully, in my opinion, using anonymized samples with some demographic or clinical data, it would be, again, that is totally personal, a lack of scientific integrity to proceed in the absence of such studies.

It is almost paradoxical to protect the sample; i.e., in quotes, according to some person and yet not have the proper scientific data on which to run your research with those very living persons, whose rights you are supposed to be protecting.

So, that is a very personal point. It does come out in the general conclusion at the end.

I also wanted to highlight the last point before I go to consent and confidentiality and access is that this notion -- it is in Holland. It came out in the 1997 position of the Council of Europe on the protection of medical data, this possibility of an informed opting out for this kind of general anonymized research or for surveillance studies or whatever, i.e., tell people what is going on and give them a chance to object to it if they to. Remember, it is not identifiable samples that are being used.

I think that is very interesting in terms of a general policy for population studies and on individual consent forms, this could also be offered to people saying the specific option for anonymized epidemiological research, would you agree to your samples being used. You cannot be identified. We will never get back to you. We will never have any kind of information.

In a way, it is like the larger scale NIH/DOE population study, where there is simply an institutional policy saying, look, this is the way it is going to be if you opt in for it. We can't do anything about it. So, I think that might be -- after all the vagaries of what you will see in the ten pages on consent and choice, might be a balanced position to take.

The conclusions on that part, on page 18, are still rather sketchy -- yes?

DR. MIIKE: Do you have any analysis of tissues that were not originally collected primarily for research but become important for research? In that side, since you usually go back and get subsequent consent, is the emphasis then on the procedures in protecting identity, et cetera?

DR. KNOPPERS: Removing identity, you mean?

DR. MIIKE: Yes.

DR. KNOPPERS: Yes. That is the position that the pathology societies would take. It is also the position of the American Society of Human Genetics. That is called retrospective anonymized research.

DR. MIIKE: In those situations where identification is important then, is there also an obligation to try to contact people? What about deceased people, et cetera?

DR. KNOPPERS: Where identification is important? Well, then you have to go to an IRB, obviously, and discuss whether the invasion of privacy that says identification would constitute for surviving family members is the intrusion on -- if you can't anonymize and you absolutely have to identify him -- is that the hypothesis you are putting forward?

DR. MIIKE: Yes.

DR. KNOPPERS: Whether the weight to be given to familiar and personal privacy -- because when you contact one, in genetics you are contacting the whole -- you know, you have got the ripple effect, it can be -- the research is so vitally important to you, you really have to balance societal versus individual familial privacy.

DR. MIIKE: Is that then left up to the individual circumstance --

DR. KNOPPERS: It depends on the country. There are laws -- most laws, and this comes right into my next part on confidentiality and access -- even the strictest laws will make exceptions for public health purposes, crime, national security, safety and so on. These are traditional exceptions to strict confidentiality requirements.

So, if in your particular research, there is a public health component that is so vital in the interest of the whole collectivity, then, perhaps, that would weigh in as an exception even under strict statutory --

DR. MIIKE: Can you give me an example of something like that?

DR. KNOPPERS: Let's see. I am trying to think of --

DR. EMANUEL: Yes. Transmissions of infectious

diseases.

DR. KNOPPERS: I am thinking what is happening right now on some of the stuff, yes. Yes. And they are dealing -- no, I won't go into it. No time.

DR. EMANUEL: I think this issue of consent actually turns out to be a core element. I want to understand -- and I apologize. I just got this. So, I haven't read it.

One of the issues for us is the trend towards what actually will fall under the anonymized rubric. Will it include, say, repeated updates on clinical status, but some kind of barrier with the investigator? Is that what is being usually put into the classification of anonymized?

DR. KNOPPERS: You mean where you are updating your research on the same cohort?

DR. EMANUEL: You may be following someone, say, with breast cancer and they keep coming into the clinic and at some point, you want to get their breast cancer tissue, but, you know, with hundreds of other women, but you want to have the latest clinical status, whether alive or dead, recurrence, not recurrence, whatever.

DR. MURRAY: I think Zeke has got his finger on an ambiguity on how the concept of anonymized has to be used and there are at least two senses. One is where the sort of base tissue sample itself has simply been stripped of identifiers.

DR. EMANUEL: You couldn't get updated clinical history versus anonymized where you are constantly getting updated, but when you actually go to analyze the sample, you separate it in some irreversible manner.

DR. KNOPPERS: That is right.

DR. EMANUEL: The investigator may never -- cannot get to that information but, say, a pathologist could.

DR. KNOPPERS: To identifying information you mean?

DR. MURRAY: That is not anonymized --

DR. KNOPPERS: That is not anonymized.

DR. MURRAY: Yes, but Zeke is correct in saying that that is -- it is used in some instances in that second sense in which he --

DR. KNOPPERS: That is traceable or identifiable. You can get back no matter how or whatever system you are doing.

DR. EMANUEL: No, no. What the question is -- the question is who can get that. The researcher can't get that, but the pathologist who holds the original sample

could get that. Do you see what I am saying?

DR. KNOPPERS: Yes, but how would the researcher contact the pathologist?

DR. EMANUEL: I go to the pathologist and say I would like all breast cancer samples and the clinical histories associated but I don't want to know who they are. And I couldn't from the demographics tell. The pathologist will still know, but he won't know which category they fall into because the researcher doesn't know and the researcher doesn't have the key to get backwards.

Now, some people have said that is anonymized. Some people say that is linkable.

DR. KNOPPERS: Linkable. As long as there is a key, it is linkable.

DR. EMANUEL: I think if the researcher can't go backwards, that is a different -- that is not linkable.

DR. KNOPPERS: Well, you might want to look at the -- obviously, then, the definition of the ASHG is not sufficiently clear --

DR. EMANUEL: Right. It is too ambiguous.

DR. KNOPPERS: Yes, it is too ambiguous. And I am not sure if the Canadian definition is any better then for you. Where did I put it? On page 12, where they -- identifiable, no problem. Everyone knows what that means. Traceable includes situations where there is access to further information. You don't have it but you can get back to it somehow, no matter how. That is traceable.

DR. EMANUEL: No, no, no. I am not --

DR. LO: Traceable by whom?

DR. EMANUEL: Yes. See, the issue is by whom. If I say January 1st, 1997, we are going to cut off. I am going to take all the clinical data on those samples and then go. But I don't know who those samples are as a researcher.

DR. KNOPPERS: The problem with that kind of a policy would be the status of the tissue would be dependent on the person and to have an across-the-board policy like that would probably make research more difficult than helpful in the sense that if you have got your tissues categorized in whatever country you are in or what kind of words you use or definitions, ASHG or whatever, then it can be used across the board, across countries and borders.

If you are saying, well, this researcher doesn't know or this research project works this way, but another research project works that way and pathologists have a different set of rules, it is not going to -- you are going

to be hindering --

DR. LO: This is an American peculiarity and it comes out of the history of HIV testing, where people wanted to do HIV testing on samples drawn in the emergency room for other purposes, but they also wanted to wait to link up with future events. You know, most of the countries in Europe said go ahead and do the study. It is important epidemiological research and just keep it -- you know, just assure confidentiality.

What was worked out here because of the discomfort of being able to link a positive test result to an individual and, yet, not inform them, was to gather the follow-up data and then strip the identifiers so that no one could go back and trace. That got the researchers out of their perceived dilemma of knowing that they had identified some HIV positive individuals but felt very uncomfortable contacting them.

They said we can't contact them because we stripped the identifiers. It always struck me as a very sort of ingenious but morally slick way of getting around it.

DR. EMANUEL: But this is an ongoing problem with large epidemiological studies, where you want the latest clinical data on them, but you also want to not have the identifiers there. The Physicians Health Study is an example, where you have stored the blood samples and you are going to do a test and you want all that clinical data on those samples. But you don't care who they are. I mean, you are not genuinely interested in the identifiability of them, but you want the latest clinical to associate with your lab study.

That seems to me to be the merging mechanism because we have all sorts of storage banks on that. Now, your claim is that most people would classify that as identifiable as long as --

DR. KNOPPERS: Right now in the United States, yes.

DR. EMANUEL: I think it is ambiguous in the United States the way it is written.

DR. KNOPPERS: Well, yes, up until about this year, I would say now it has become ambiguous, but as of 1995, that would definitely have to be --

DR. LO: The policies are not how you categorize it but what your moral responsibility is if you as the investigator with this anonymized data set find a result that maybe is of potentially great clinical import to

someone in your population. What is your obligation to try and trace the link backwards so you can identify the individuals at risk?

DR. EMANUEL: I think there are several things. One is what procedures do you need to go through to be able to do the study? Do you need IRB approval? Do you need informed consent of that person, et cetera? That is one issue.

No, on these you can't trace back because once you got it as a researcher, say this vial comes out positive, you have no idea in the 40,000 people who that is. You don't and the pathologists can't go backwards either.

DR. MIIKE: Does somebody else know?

DR. EMANUEL: No, the pathologist couldn't go backwards.

DR. KNOPPERS: Well, then it is anonymized.

PARTICIPANT: But there is a sample that is not anonymized.

DR. EMANUEL: Exactly. The pathologist still has a sample that has all the clinical information, but because you have 30,000 samples, you don't know which person that is.

DR. LO: You may actually be able to link because you have got 40,000 names with different bits of clinical information. You could probably write a computer program that could match that back to a pathologist's database. It is probably not that hard to trace.

DR. COX: But, see, you are focusing on the researcher here and part of the problem is is it is the people who the samples came from, too. So, if up front they knew that this was going to be research for which the information would never come back to them, that is fine. But that is really never clarified.

So, the pathologist has the possibility of doing that, right? But he or she doesn't because it is hard to do, but the possibility is there. So, so long as the possibility is there, then there is always the option if the person says that they want to know. And this has actually happened in the case of these retrospective breast cancer things.

DR. KNOPPERS: I am not sure the pathologists want that kind of responsibility either.

DR. COX: Well, some do.

DR. LO: Well, again, it is when you leave it open to the individual choice of a pathologist versus the, you know, genetic researcher, then what expectations should the

subject who donated the tissue have about what is going to happen to them in terms of --

DR. EMANUEL: I think this is a very important case that we are actually going to have to try to illustrate because I am not -- I am still not sure we are all talking about the exact same thing and there may be fine points here that need to be --

DR. MURRAY: There actually has been a proposal. I don't know if everyone got the article for a kind of one way flow of information.

[Multiple discussions.]

DR. MIIKE: When you begin an experiment and you have identifiable and you are going to decide whether you are going to have them as anonymized versus identifiable with the researcher not knowing, is it reasonable to make a decision at that point in time about what you are going to do? Are there examples that come in you folks' experience that you might have anonymized this and then you come out with a result that is very important, unanticipated results that are important to get back to the original -- to the actual person giving the sample?

DR. EMANUEL: One story with all those people who had -- you know, where they got the samples from Paysachs(?). I don't know. There is obviously some ambiguity as to how important that would have been, but --

DR. LEVINSON: No. In any case where a gene is identified and later on a treatment or prevention may be identified and at that point, it becomes important to be able to go back to that person.

DR. MIIKE: But there are examples where they are going to try to find whether there is a gene associated with a particular condition. Once you get the gene identified, then I say it is a different question. So, I am just asking the question whether this issue about whether it should be anonymized or not identifiable to the researcher, but somebody looking back gets decided at the initiation of why you why want to do the research in the first place and then are the examples where that system falls apart so rare or nonexistent that we don't have to worry about it and we have got the solution or what?

DR. EMANUEL: I don't think the answer is clear.

DR. MURRAY: Yes. We probably need to move on to the next point. Here, I am in agreement with Zeke that there is an important ambiguity here and maybe something important for the future of research with human tissue.

It is not entirely clear yet. Maybe what Elisa

Eiseman tells us in the second hour today will help to clarify some of that.

DR. KNOPPERS: I will leave that, but I --

DR. MURRAY: One other thing, Bartha.

We started at 3:10 instead of at 3:00. We had Madame Lenoir here and that took a little time. Can we go to at least 5:15? Is everybody in agreement on that?

DR. KNOPPERS: I am leaving at 4:30.

DR. MURRAY: We will finish with you by 4:30, but we may go -- if it is okay, go to 5:15.

DR. KNOPPERS: This point is important because you are not going to be able to have a general opting out. In other words, you are not going to have at a population level or familial or deem level or by disease level or whatever group you want to call it, opting in for anonymized epidemiological if you are going to be able to link back somewhere and you are going to create look back, recontact, notification and all kinds of other legal obligations that, you know. So, you are going to have to really think about this last issue.

Okay. Confidentiality and access, this part is a little less complicated. First of all, no matter whether international or regional or national, the general move towards full disclosure is still at full bloom. Like the consent multiple choice phenomenon, however, I think it is pretty well reached its -- what do you call it -- I am thinking in French again --

PARTICIPANT: Nadir.

DR. KNOPPERS: Thank you. In that -- with the concomitant result that we now have the right not to know. Of course,you need a minimum of information to decide what you don't want to know. It is impossible to talk about a right, which is still a nascent right by the way. Don't think of it as a developed legal right. It might be an ethical notion. It is still a nascent legal right and should be based on some minimum amount of knowledge. Otherwise, you are undermining the very essence of it.

So, full disclosure, a diminution -- that is French again, sorry -- and decrease, especially in European countries of what was more traditional there, which was the therapeutic privilege. I think genetics has finally killed off pretty well the therapeutic privilege, even though it remained in a lot of their codes of deontology in European countries that physicians may hold back grave and serious information so as not to trouble -- that may sound strange to your ears, but that has been very much an ethos in

European countries.

So, we have the full disclosure, the emergence of this, in quotes, right not to know, and death almost of the therapeutic privilege. And I think definitely with genetics that will do it.

There are a whole bunch of things -- what is in the paper, there is enough details in there. Turning then to family members, okay, so the patient has a right to know, not to know, access to the results and so on if they want to, et cetera, to be recontacted in the future or not, to be notified of incidental findings or not and so on. That is under consent and choice.

What about family members? Well, this is really interesting stuff and certainly an area that needs more research. Do family members have any, in quotes, rights to the DNA of other living family members? We will get to dead ones in a minute.

The international regional and European positions are much more in favor of an intrafamilial obligation to share information and samples. This would -- this is blood relatives, though. All right? This excludes -- they haven't gone as far as spouses and common law partners and so on. It is definitely very much more of what I call a familial ethic or mutuality within families.

So, this notion of intrafamilial disclosure is definitely growing in the European context. One reflection of not only intrafamilial, one reflection of this phenomenon is that even here the present commission already in 1983 when it came to physicians who were confronted with patients/research participants, who refused to communicate with family member -- because if there is access but there is also informing. It is almost like a corollary kind of intrafamilial reciprocal obligation.

Already in 1983, your presidential commission set, if you like, the standards for under what conditions, where there is such refusal, a physician would not obliged to warn, but could if certain -- the four conditions, which are in the paper, I won't repeat, are met, considered at least to be an ethical obligation and maybe a legal defense. I am not -- privilege. I am not going to go into all the legal details of it.

These criteria of the presidential commission have been appearing in different forms in official policy statements around the world. Has to be a serious -- first of all, there has to be refusal, has to be serious, high probability of occurrence, imminent sometimes or at least

highly foreseeable, treatable, preventable, et cetera.

I think the statement that will be coming out this fall at the American Society of Human Genetics on physician disclosure will, again, pick up on that thread. As you know the Genetic Privacy Act sees no such obligation and no -- you are, in fact, prohibited from giving family members access to your patient/participant's DNA unless your patient/participant is dead. And that suddenly changes the rights of family members.

This is an exceptional physician --

DR. MURRAY: Bartha, you are talking about Georgiana Strapt(?) Genetic Privacy Act --

DR. KNOPPERS: Yes.

DR. MURRAY: -- which I don't know how many states have adopted --

DR. KNOPPERS: 11.

DR. MURRAY: -- versions of it. 11?

DR. KNOPPERS: I think so. That is what I read.

DR. MURRAY: I didn't realize it was that many. Okay. Thank you. I just wanted to get that clear.

DR. KNOPPERS: Various parts of it -- it has never gone in in toto anywhere. As I said, the property thing as been taken out. You see, it is for lack of -- well, it is there. Put it that way. How is that?

Interesting also in some European countries -- I won't go too long on this -- is the failure to rescue. Some countries of Napoleonic tradition have a duty to rescue where someone's life is in peril and it doesn't put your own life in peril. And could this be used, for instance -- the French brought this up, as parents having an obligation to rescue their children by sharing the DNA and so on and so on. So, I didn't go very far. I will be drawing my own personal conclusions in my next draft, but I didn't want to push my own opinion on this.

In Quebec, we now have by law an article that says after death, you -- even if the dead person has refused during a lifetime, there is automatically access to DNA for familial genetic conditions. The codes of ethics of various genetics bodies have said that even while alive, patients should be given the option of choosing whether a family member should have access or not. So, at least it should be on the consent form.

Should there be above that a positive obligation to share, that is another issue. I would say "yes." I know Wirtz(?) and Fletcher in their WHO guidelines say that the -- it is family property, the DNA that family members share.

Insurers and employers, I don't really think you need to go into the whole situation.

DR. MURRAY: Unless there is anything that --

DR. KNOPPERS: I would rather have five minutes to go to my general conclusions.

DR. MURRAY: Okay.

DR. KNOPPERS: Let's just say even in countries that have universal health care, insurance is a problem because of life and disability insurance. Okay? So, you are not alone in your struggles with this.

As to researchers and collaboration between researchers and access to samples of other researchers or sharing between researchers, WHO, the position of the advisers, which is going to become maybe an official position in December when that advisory report is going to be discussed to become an official report, says that if identifying characteristics are removed, researchers should be able to share samples. We get right back to the whole business again of this -- anyway.

And that population screening should be possible on a population basis for surveillance or for epidemiological studies if samples are made anonymous. This is so that the state, in quotes, for public health planning can follow incidence and prevalence. The reason that this is very important and why they suggest an opting out, at least tell people that this is happening and then if they want to opt out, they can say I am out, is -- take my own province. We have a new article saying that any sample since 1994, removed during routine care that is going to be used for research, undefined research -- it didn't say what kind -- you need a written consent.

So, the positivists, the legal positivists, took this to mean any kind of research, including surveillance, epidemiological and so on. So, all HIV data has stopped. We don't know what the incidence or prevalence or increase or decrease of HIV is in our own province because we can't touch samples, even for epidemiological surveillance to studies without consent. So, it is very bad when you have that kind of approach.

DR. MURRAY: Bartha, could you include that example in a paragraph in the next draft?

DR. KNOPPERS: I can't because Quebec is not a country, so I couldn't put it in in my bibliography.

[Laughter.]

PARTICIPANT: Do we know how you voted in the last election?

DR. KNOPPERS: If my husband heard this --

DR. EMANUEL: Could we wait just a few more weeks and maybe --

DR. MURRAY: -- is a member of the --

DR. KNOPPERS: Yes, he is elected politician of the party for Quebec recognition as a country. But I could not --

DR. MURRAY: This is a domestic issue.

DR. KNOPPERS: So, the state, again -- I mentioned it earlier. There has always been traditionally -- now, this is something to watch, this kind of exception, this traditional collective interest, public health, secured exception, which has been around for a long time, is now under suspicion because of genetics again, because it is being used in the criminal context for, you know, banking recidivists and so on. It is all -- and the flow over into public health, a legitimate public health policy, which is now also seen as suspicion because you see the state is keeping genetic profiles and so on and so on, is something to really reiterate the public health rationale.

It needs a boost and it needs greater elaboration and greater detail. People don't buy public health because they don't know what it means anymore. So, I think in the genetic context, it is going to be very important for you to deal with that issue.

I want to go straight to my conclusions on page -- at the end, then, Tom, just so --

DR. MURRAY: Sure.

DR. KNOPPERS: Page 32.

DR. MURRAY: Your conclusions on the confidentiality section or for the full paper?

DR. KNOPPERS: Well, the confidentiality section, I think, is -- there are six of them or five actually.

DR. MURRAY: Yes. General conclusions on 32.

DR. KNOPPERS: We will go straight to the general.

Okay. The first is -- and this is an -- we are now at the stage where we have to integrate human genetic research into mainstream medicine. This is also my last conclusion, which I will get to in about two minutes -- in order to normalize DNA banking, genetic testing and genetic information. So, how to do this and the reason we are having great problems is not only because of the historical context relation to genetics and so on and some of its specificity in that it is familial and not just personal, but also because of commercialization and because of informatics.

When you can put demographics, informatics and genetics together, you are in a new re-creation, if you like.

I mentioned the sui generis, which I think it is very important that we end the property/person debate, that we remind ourselves constantly of what the differences are between the two. They have very important symbolic value, but let's get on with protecting what the human subjects or participants, I prefer to call them, and the material and the researchers and so on and get away from either the reification or the sacralization of the sample, as I say.

I also take the position that both reification and sacralization of the sample are reductionist in that the first disregards the human source, the human. Everything becomes a sample source. Property interest, but still a sample source, while the latter raises DNA to a higher status than that afforded to the living person, whose DNA, while unique, is also shared.

Both of them might harm epidemiological and public health research. I would argue that an anonymized sample is no longer related to a particular person and that, perhaps, is opting out with notification, general notification, to the public at large and specific notification in research protocol might be the way to go.

The reason you need the general notification is, obviously, for leftovers during routine care. You need specific notification during research protocol, with opting out in both situations.

And insurance and employment, I will be coming to my own conclusions in my final, final paper. However, since it was not under my mandate, I didn't go into further detail in this paper. I do argue for international, at least your mandate is national, so let's say national standardization of core elements of coding, anonymization, conditions, length of storage and this new -- and the question of destruction of samples, which pathologists find an anathema and which others find an expression of free choice and individual choice.

The idea of being able to physically withdraw samples is nonsense. Withdrawing from participation, obviously, is very important in terms of saying I want to stop here; I don't want to go further. So, you can't use that person's sample anymore. But anyone who has ever been in genetic research knows you can't physically sort of walk out with your DNA, so to speak.

My conclusion then --

DR. MURRAY: I am sorry, Bartha. That is just a little mysterious. I mean --

DR. KNOPPERS: You want to go home with it?

DR. MURRAY: No. Without committing -- I am not sure what I think about it, but it seems to me if you said you have got my sample, I want it destroyed, that is at least a meaningful thing to say.

PARTICIPANT: No, no, no. She is saying something different, withdrawing it.

DR. KNOPPERS: I said withdrawing. You can opt to have it destroyed, even if you might say, oh, we need it. It is so important for mankind or whatever. That still is a very personal choice. But the idea that some people are now saying not only consent or refuse to continue to participate, but you should also be able to physically withdraw.

DR. MURRAY: Like it is my x-rays.

DR. KNOPPERS: Believe me, people have asked.

So, my conclusion is to somehow avoid either genetic specific legislation or human rights general legislation in this particular context of research with genetic samples and strengthen the provisions currently found within the physician/patient relationship with respect to confidentiality, respect for patient integrity, respect for choice, respect for the patient within a family unit and to, as much as possible, if you can in your work and your conclusions, keep it within that formerly sacrosanct and, hopefully, still sacrosanct relationship and strengthen and reaffirm the deontological and legal, if there are any, safeguards of genetic information, genetic samples and research within the medical context.

One, it is a good barrier against commercialization. Second, it is the most personalized context and the most real one for the patients.

Are you not following me, Tom?

DR. MIIKE: Do you consider the Carleton Rocken(?) pathologies revised statement and the redefinition of what -- genetic information to be not productive or contrary to what you are saying?

DR. KNOPPERS: If I may say so, I think it was in reaction to the earlier -- I think we need to find a middle ground between what the pathology societies are saying, for whom it is just stuff, and the first statement that came out from the first NIH one in 1995, that literally, you know, raised the sample above persons.

DR. MURRAY: I take it you said you needed to

leave at 4:30 because you need to leave at 4:30 to get somewhere.

DR. KNOPPERS: Well, actually, if I could have flown back Air Canada, I could have stayed longer, but since I have to fly on government rates and go to Pittsburgh first, I have to leave.

DR. MURRAY: Right. We have about two more minutes before she needs to leave. Does anyone have any other questions you want to ask her?

We will have questions and I just want to -- so, I want to keep the communication links open. What is the best way to reach you?

DR. KNOPPERS: E-mail. Don't try call -- I don't answer --

DR. MURRAY: We will make certain that if you don't all have Bartha's e-mail address that you will and you can then communicate with her directly or through our --

[Multiple discussions.]

DR. EMANUEL: The one question I have for you is the sort of increasing separation of the sample from that relationship. I mean, I guess one of the big concerns for many people is the fact that, you know, you go in and your surgeon takes out a piece of tissue and then a couple of years down the line someone else wants that sample. They have come up with a new test or they want to investigate all people with this disease or whatever it is and it is not clear to me that your call for strengthening the protections in that relationship really are going to do much for this other context, one.

Two, there is the other situation of massive now, 40, 50,000, 100,000 person epidemiological studies with interventions, but that have now banked samples that are quite useful for a whole variety of things, often not anticipated at the start or new tests that come along even in that same disease.

I am not sure the model you suggested necessarily apply in either case.

DR. KNOPPERS: No. You are right. It would be a de novo kind of start for those samples already banked and left over that people -- it used to be that you abandoned all your debris on entering like residue elicta(?), the Latin expression for it. And what to do then about those already banked and already there. The only way I think you could use them would be to tell the public that samples -- we need them for epidemiological or genetic research and so on. However, we will remove -- you definitely have to

irretrievably, no little keys anywhere, anonymize them and, however, that may break somebody trying to build a pedigree and needs one little last identifiable source, otherwise, at the current state of affairs, you simply can't do that, even though the intention of those persons was to abandon the -- when it never entered their mind in 1950s, sixties or even seventies, that they were ever going to be able to have any kind of control over abandoned body parts or cells or bloods or whatever.

Starting new, I think the opting out generally for routine care leftovers is a good approach, that the Dutch have put into their civil code. And I think for research protocols you should offer a choice.

DR. EMANUEL: One last question. Did I get you right, you would not distinguish doing genetic tests on the stored tissue from other kinds of medical tests?

DR. KNOPPERS: No.

DR. EMANUEL: I just wanted to make sure.

DR. KNOPPERS: So it is genetics, so what?

DR. EMANUEL: I agree with that. I just wanted to make sure that we had --

DR. MURRAY: We could keep you here but we don't want you to miss your flight.

DR. KNOPPERS: No. The next version you will get is going to be more highly opinionated simply because I am now going to start preparing it for inclusion in a book. I will also correct any errors. I will check all footnote numbers and so on to make sure I have got eery country correct and so on. I think there is enough basic information to keep you going for awhile.

DR. MIIKE: One last question. If you get tissue and it is totally anonymized, non-traceable, et cetera, you still would want that person to opt out of future studies. Is that correct?

DR. KNOPPERS: Give them a choice to opt out of?

DR. MIIKE: Yes.

DR. KNOPPERS: Yes.

DR. MIIKE: Why is that?

DR. KNOPPERS: They are in a research protocol? These are people in a research protocol?

DR. MIIKE: Let's make a hypothetical where there is no harm ever going to come to that person, no tracing whatsoever, but it may be used for research. You would still require --

DR. KNOPPERS: If you are in a research protocol, you are in a different situation. You are in a relationship

that is of a different nature, where the obligations are more of communication, of getting back and so on, are much more intense, of a higher level of communication. There you would have to give, no matter whatever, a choice to be anonymized or forever anonymous or whatever.

When I said anyone going through a hospital where you are already consenting to have that blood or urine or whatever it is removed, you don't opt out in writing. You are told that unless you say something, this will be used in anonymized research because -- that is different. And there, you know, there you would have access to -- unless someone actually, which they might do -- I mean, we do have --

DR. MIIKE: Well, take that example, would you still find it necessary to say unless -- whatever, do you still need --

DR. KNOPPERS: Yes, just in case.

DR. MIIKE: And why is that? Is it because there is something special about our body parts or our genes or what?

DR. KNOPPERS: That is not my personal opinion. I am saying as a public policy position, that is probably -- one, it is best to be transparent, even in the medical situation. If people find out later that surreptitiously all bloods during the last five years at Mass General had been shipped off to some project in Denmark for studies on who knows what, it would undermine the trust that you have when you enter into the general consent to medical care.

DR. MIIKE: Well, I am just raising that in the sense that people use my social security number for any number of purposes. They sell it. They sell my addresses and things like that. So, I am sort of looking for an underlying societal reason why -- why we feel so special about this. Is it because --

DR. KNOPPERS: Well, again, you are not going to the hospital because you want to. I mean, again, it is not as -- it is not the same as a research relationship, but you are not there by -- if you want to go give blood --

DR. MIIKE: You know, if I have to drive in the United States and they happen to use my social security number for my driver's license -- there are any number of things in this society that I have to do. I mean, you can -- we can quibble about whether I don't have -- I don't have to go in the hospital. I can get my tumor on my leg, et cetera, but I am just asking sort of a philosophical question, I guess. I mean, why is that? I mean, is it

because that is something to do with our bodies or what? And, yet, at the same time, the law has been such as that when I die, I am just a piece of chattel. In the old days, it was my family who could do what they want with it. Right? I mean, you have to override -- in those days, I had a personal opinion. I want to be cremated and your mother says, oh, no. I want to bury you in the family crypt.

DR. KNOPPERS: That still happens, by the way.

I think the point is is when you are entering a health care institution, you are not thinking about research and patents and products and tests and implications of what might be found for family members and so on. So, it is one respect for individuality and integrity, which is in all medical care, but it is also the transparency of what is actually happening in that institution. If it is a general policy, then unless you say something -- and I am talking consent forms I can research. This will be going on and the following protections have been put in place.

I myself don't hold -- I feel, you know, with the DNA we share with the plants and animals, I have personally no particular attachment to my DNA, but I can see where we would have to put that protective policy in place for those who do in order to make sure that the research can go on because it is the lack of that transparency that is currently going to be harming genetic research.

DR. MIIKE: So, it is more a reaction to how you want to use it rather than a protection.

DR. KNOPPERS: I think it is a balanced approach to the conflicting physicians and the different cultures and values, which I might not share, but which I recognize as being important.

DR. MIIKE: By the way, you have no idea what my personal opinion is.

DR. KNOPPERS: Well, you know mine now.

DR. MURRAY: Bartha, thank you.

DR. KNOPPERS: You are welcome. Good luck. I can come back if you -- after grant-writing season. Please wait until October 10th.

DR. MURRAY: We gave Elisa a very simple and easy task, which is to find out everything there is to know about how many samples there are, tissue samples there are, and under what sort of circumstances they are gathered, what sorts of organizations hold them, under what conditions and how they are used. This is -- we will call this your interim report.

Agenda Item: Tissue Samples and Sampling

DR. EISEMAN: Which I have only been working on for about two weeks. Although I have to admit I was able to find a lot more information than I thought I would in the short time that I have been working on the project.

So, as Tom just mentioned, the questions that I was asked to answer kind of fall into the general category of who, what, where, when, why and how. Where are these samples? What are they used for? And more specifically -- I am sorry. Everyone should have a copy of these slides. If you don't, there are some extras that Henrietta has.

So, more specifically, the questions are -- I kind of phrased them in the context of who, what, where, why, when and how. And those are here. Who are the sources of the stored tissue samples? Who has access to the samples? For what purposes are stored tissues used? What identifying information is kept with the tissues?

Where are tissue samples stored? In other words, what institutions, where physically are they? When are stored tissue samples discarded? Why were the tissue samples originally collected versus the question up above is for what purposes may they now be used for?

How many tissue samples are stored in the U.S., which I am not sure we will ever get a concrete answer to? And then, lastly, how are the tissue samples stored? Physically, are they in the freezer or in a cabinet?

So, the first thing that I tried to do is kind of get my hands around where are tissue samples stored, what types of institutions. This is what I came up with. It is, obviously, open to suggestions if anyone has any other ideas, but I tried to be as comprehensive as possible.

One is at military facilities, which includes the Armed Forces Institute of Pathology, as well as medical centers, military medical centers, and also VA medical centers.

The second would be at forensic DNA data banks, government laboratories, such as NIH. At the NIH, there are several sample banks, tissue banks; DOE, the CDC, which is involved in NHANES, which is the National Health and Environmental Health Study, as well as under "Government," I have included state government, the state public health labs that do a lot of the prenatal -- I mean, the newborn screening tests with Guthrie cards; at diagnostic pathology and cytology labs, which I have differentiated from university and hospital-based research labs.

And then there is commercial enterprises, like tissue banks, DNA banks, and I have also included within

this, pharmaceutical and biotech companies that may have tissues in storage for both research or that have come from clinical trials.

There is also non-profit organizations and blood banks. You will see, hopefully, through the talk that I have included all of these.

So, now on to some specifics. Basically, I am going to start with at the top of the list that I just showed you because that is where I was able to gather the most information. Of course, the top of the list is the military, where you would expect that this information has been recorded and is -- and not expected that it is so readily available, but it was, which was very nice.

So, I have divided the military into two sections for information that I have now under the Armed Forces Institute of Pathology and we are still working on gathering information on medical centers and VA hospitals.

Within the Armed Forces Institute of Pathology, there is the National Pathology Repository, which is the world's largest pathology repository. It has collected over 2.5 million cases, starting since 1917. Those 2.5 million cases have actually been divided up into huge numbers of actual samples, over 50 million microscopic slides, 30 million paraffin blocks and 12 million preserved wet tissue samples.

And they say that they are collecting about 50,000 new cases per year. So, it is a huge source of samples.

In contrast, the DNA Specimen Repository is a repository of samples from enlisted personnel. Jennifer, who has been working with me on this, was able to get up-to-the-minute data. As you can see, at 9:28 -- but as of 9:28 this morning, there is just 2 million blood and saliva samples stored in this DNA repository. And there are accruing samples at the rate of 10,000 specimens per day. So, again, it is a huge repository of samples.

A lot of this is collecting bagged samples. So, when you enlist and when you start, you actually give a sample, but they also have to cover people that are in the service now. So, this accrual will eventually slow down once they kind of catch up with people who are already in the service.

Right now, the DNA -- well, actually, I should say as of 1996, under new regulations, these DNA samples are maintained for a period of 50 years and, again, under these new regulations, there is an option for servicemen to ask for their samples to be disposed of only after their service

to the military is finished.

So, who are the sources of these samples? The National Pathology Repository has both civilian and military sources from throughout the world. So, basically, they can be deposited from anywhere. This includes all of the branches of the Armed Services, as well as the Veteran Affairs hospitals, other federal agencies, such as the Justice Department, Public Health Service.

The civilian samples are submitted under the Civilian Consultation Program in cooperation with the American Registry of Pathology. And, again, as I said, there are foreign contributors.

For the DNA Specimen Repository, as I mentioned, it is all military inductees. That includes both active and reserve personnel. This also includes civilians and foreign nationals, who may be working with the United States in areas of conflict. So, it is not just limited to domestic personnel.

For what purposes are the stored tissues used? The National Pathology Repository is mainly used for consultation, education and research and pathology. Some other areas is to study unusual tumors that they may have samples of and it also can be used as part of a public health surveillance system to study new emerging infectious diseases.

The DNA -- so, it has multiple uses. Whereas, the DNA Specimen Repository is meant to have only one use and that is to be used as reference material for identification of remains. In the DNA Specimen Repository, the blood and saliva is stored and the DNA is not extracted until it is needed for remains identification.

So, who has access to these samples? The National Pathology Repository is very open to collaboration. They freely loan samples -- I shouldn't say "freely." I should put a disclaimer on that. The samples can be loaned out to individuals or organizations, as long as they have consent from the depositor. The depositor can get their samples back for follow-up studies on patients as well.

The DNA Specimen Repository, the samples cannot be used by anyone without consent for purposes other than identification of human remains, except for where subpoenaed for investigation or prosecution of a felony.

DR. MURRAY: Lisa, am I correct that all samples are identifiable samples?

DR. EISEMAN: That information, we don't have a conclusive answer on. They are coded by diagnosis, but they

also do contain patient information and for collaborative research, I am not positive how the samples are sent out.

DR. EMANUEL: And they may not even have name tags.

DR. EISEMAN: I know that they do have names because a pathologist, who has deposited a sample can go back and say I need this sample back to follow up on a patient. So, I don't know if all of them still have names or if there is a portion that have names and some that don't.

So, how are the tissue samples stored? As I just mentioned, the material is coded by pathological diagnosis and, as I mentioned at the beginning of the discussion of the military, of the National Pathology Repository, but there are multiple forms, microscopic size, paraffin blocks, et cetera.

The DNA Specimen Repository, three DNA specimens are collected from each serviceman; two blood samples and one buccal smear, which is some of their T cells. The two blood samples, one is stored in a pouch in the medical record and the other is stored in a vacuum-sealed bag and placed at minus 20 degrees at the repository.

The buccal swab is fixed in isopropanol and stored at room temperature at the repository. These specimens are obviously identified and include a lot of identifying information.

DR. MIIKE: [Comment off microphone.]

DR. EISEMAN: No, not all samples from military medical centers are at the repository. They do maintain their own repository --

DR. MIIKE: [Comment off microphone.]

DR. EISEMAN: That is my understanding and we did check into that. That was a question that we both had as well. We are not clear exactly how -- which exact samples get transferred to the repository versus which ones stay at the hospital. But I can tell you that Tripler Wood maintained its own storage of pathology samples and not all of their samples would be sent to --

DR. MIIKE: [Comment off microphone.]

DR. EISEMAN: I don't know. That is a good question. I do know that as some of the military medical centers are being closed down, that those samples are then transferred to the repository.

Now, I am going to move on to the forensic DNA data banks. And don't worry because, like I said, the military has the most information. So, I am not going to

drag you through all that information on each one of those. But I did want to talk a little bit about some of the other places where samples are stored.

Forensic DNA data banks, the information is actually stored as data, not the actual DNA sample itself. So, it has gone through the restriction digest and the data is in the computer.

By September 1996 -- and this is information obtained by Jean McKuen(?) -- 32 states had begun to collect blood or in some cases, saliva from convicted offenders and actually 40 states had state statutes in place by September 1996.

Nationwide, these samples number up to around 380,000 and about half of them, not quite half of them, 30 percent of them, 116,000 of them had been actually analyzed and were entered into the DNA database.

DR. EMANUEL: [Comment off microphone.]

DR. EISEMAN: Correct.

DR. MURRAY: That is not stored tissue.

DR. EISEMAN: It is genetic information.

DR. EMANUEL: Yes, but it is not like if I wanted to go back and, you know, do a DNA study, I could.

DR. EISEMAN: No. It would only be for identification purposes.

So, the DNA profiles prepared from the samples have already been valuable in tracing biological material found at crime scenes. Again, by September 1996, the data banks had already achieved cold hits in at least 58 cases; "cold hits" meaning a sample taken at a scene was analyzed and was found to match up with a sample of a criminal that was in the database without any other connection, not knowing who the perpetrator was.

Then in at least 80 instances, DNA data banks have been used to establish associations between two or more unsolved cases. For example, in Minnesota, they were able to take biological material from 18 different crime scenes and link them all together to show that it was the same person who committed all those crimes. Unfortunately, I think, in that case they didn't have a prior conviction, so their data wasn't in the file. So, they couldn't identify the perpetrator.

Okay. The state public health labs that do newborn screening -- this is the Guthrie card question -- I do have some numbers here but it is not a concrete number, like 2.5 million, because it depends on the state and it depends on how long they store the tissues for and how

populace the state is.

So, I have kind of ranges for you. The majority of labs have accumulated less than 500,000 cards over the years, although, as you can see, seven have greater than 5,000 and the one that has the most is a collection of 6 million Guthrie cards in their collection.

The number of cards collected over a year's time range anywhere from 10 to 500,000 and the example here is in California. Almost all the children born in California are tested and there is about 550,000 children born each year in California.

So, what are the purposes? The obvious one is to screen newborns for inborn errors of metabolism, such as phenylketonuria, cystic fibrosis, sickle cell anemia. There is actually a list of eight to ten different screening procedures that are done and it varies from state to state which ones are done.

But the other thing that they have been used for is a resource for population-wide genetic epidemiologic studies, which we were talking about earlier.

Who has access to the samples? I kind of answered that in two ways. One, who has immediate access within the lab, and that ranges from six or fewer people to greater than 20 people versus who has access on the outside, what third parties may have access to samples.

Again, this is information from a paper by Phil Riley and Jean McKuen and in their study, they found that the vast majority of laboratories would not give access of identifiable Guthrie cards to insurance cards for employers. However, several labs would give access to law enforcement or other state agencies, such as the state child welfare agency.

There is a lot of information on this slide and just to summarize it very quickly, each state has its own way of storing the sample. It ranges anywhere from sticking it in a cabinet to putting it in a special box and putting it in the freezer, putting it in a warehouse or a basement. So, these are all over the place.

DR. EMANUEL: But they do contain a lot of information.

DR. EISEMAN: Yes, they do. They do contain identifying information, such as the mother's name and address, the hospital of birth, the baby's medical record number. However, it is easy to cut out a spot from the Guthrie card, a spot of blood, and use that for what would be considered -- I don't know now -- anonymized or -- for

epidemiological purposes or other.

Just an idea of how long different states keep cards. There are 53 listed here. That is because it includes the District of Columbia, Virgin Islands and Puerto Rico. Forty of the states do screen their cards for some length of time, ranging from one year to indefinitely; whereas, 13 of the states discard their cards within several weeks or months.

Just a little bit on diagnostic pathology and cytology labs. There is a directory of DNA diagnostic labs called HELIX. Again, Phil Riley and Jean McKuen did a survey of these labs and I am going to present just a few of their findings.

But basically, there was 148 labs listed in this directory as of January 1st, 1994; 137 of the labs were academically based or within government agencies; whereas, 11 were commercial labs.

Again, it really varies, depending on the institution, how many samples are stored, ranging from less than a hundred to over a thousand, well over a thousand. And they are stored for various reasons. The main two reasons are for service to referring physicians or for research purposes, such as gene mapping.

I have just listed a few that I have come up with and here is where the data gets really soft. Actually, there isn't any numbers at all for you. That is with the university and hospital-based research labs. I think it is going to be quite difficult to get our hands around how much is really out there. Academic institutions basically save things forever and there are multiple different storages in universities and hospital-based research laboratories. There are some concrete or more defined, I should say, tissue banks at some of the universities and I have just listed a few here.

There is a couple at the University of Michigan, the Human Breast Cell/Tissue Bank and Database. There is also a skin bank at Michigan. The University of Maryland at Baltimore has a brain and tissue bank and the University of Pennsylvania has a bank for ovarian tissue.

So, I think those types of places we will be able to get better information about, but when you are talking in general at a university, it is going to be quite difficult. I think the way we plan to attack it is to try to call some different universities, big universities, like Harvard versus smaller universities and just get a general idea of what they think they have in their stores or at least a

general idea of new cases -- like in the pathology labs, new cases that they get every year. They should be able to give us a number for that. That is about as concrete as you are going to get there.

PARTICIPANT: [Comment off microphone.]

DR. EISEMAN: Yes, I think probably a lot of places keep them forever.

I did talk to Fran Pitlik(?), who is from the American Society of Investigative Pathology, and she kind of gave me some ball park figures that pathology departments at a major medical center may receive anywhere between 10 to 25 thousand specimens a year. So, therefore, nationwide, you can kind of estimate that there are millions of specimens collected a year.

PARTICIPANT: -- by the number of admissions for surgical procedures would give you some sense as to what that sample --

DR. EISEMAN: Well, the pathology lab should have a number. Usually, it is the year 1997 and then the case number is how many number of cases that have come in.

For commercial enterprises, as I mentioned at the beginning, I kind of divided it into tissue banks, DNA banks and then the pharmaceutical and biotech companies that are using these samples for research. Some of the tissue banks and DNA banks would be considered biotech companies, but I tried to make a distinction between a biotech company that does research versus a biotech company who is in the business to bank tissue.

I have just given some examples here. In 1992, again, Phil Riley and Jean McKuen, who have been doing a ton of work in this area, did another survey of 11 biotech companies that bank DNA and the estimate at that time was that there is probably less than 10,000 samples banked in commercial DNA banks in the United States.

I think the difference between 1992 and now is very large and we want to try to get some more information at least from those 11 companies that were originally contacted to see how big their stores are now.

DR. MIIKE: What is their purpose?

DR. EISEMAN: A lot of purpose is for storage for gene linkage studies, where families will deposit their DNA for use in linkage studies within their family. It is also used for identification purposes. Parents will submit samples of their children in case of an abduction.

PARTICIPANT: I have seen those ads on the Internet.

DR. COX: It is very interesting. I mean, the linkage thing from a commercial point of view is very interesting because almost no family is big enough to get any information. The family doesn't know that.

PARTICIPANT: [Comment off microphone.]

DR. EISEMAN: I am sorry it took so long to get to the answer to your first question, Tom. But some examples of non-profit organizations is the Coriell Institute for Medical Research up in New Jersey. It is a huge tissue bank of mutant cells.

The Rocky Mountain Multiple Sclerosis Center Tissue Bank and there is a Northwest Tissue Center. Again, this is not complete and it is going to take some digging to try to find out what else is out there.

I have to admit that this stuff under "Blood Banks" was my one big surprise, one that I didn't think of. I had thought of blood banks, but Jennifer today called the American Red Cross and found out not only do they bank blood, but they also have a tissue bank. They store cadaver tissues for transplants and it is in the consent that that tissue may be used for research or education. At least at the Northeast Area Tissue Services, it is not routinely used for research at this point, but may be available. So, it is a potential tissue bank.

They estimate that just in the Northeast Tissue Bank, which is one of six and it is probably the smallest of the six tissue banks run by the American Red Cross, there are thousands of bone, skin, connective tissue and heart valve samples.

On the blood bank side, as you can imagine, there is a lot of blood banked over the year. The Red Cross is responsible for collecting about half of the blood in the United States and they collect -- well, they collected in 1996, about -- almost six million donations of blood. They estimate that there is about 20,000 units of blood stored frozen in the United States at any one time.

They do make available platelets and red blood cells. When they have expired, they will sell those for research.

DR. MIIKE: But these are not banking in the sense that we think of banking. They are just sort of like collecting and distributing.

DR. EISEMAN: Mainly, their purpose is for collecting, distributing and, as a matter of fact, they try not to hold the blood in their banks for more than three days before they give it to hospitals, but that blood does

sometimes expire. Platelets have a shelf life of five days. Red blood cells, depending on the preservatives, can range anywhere from 21 to 42 days and if that blood does expire -- or the platelets or their blood cells do expire, they will sell that for research. So, it, again, is a source of material for research.

DR. COX: Can people get identifiers with that?

DR. EISEMAN: I don't think they get identifiers when it is sent out for research.

DR. COX: But if they ask -- normally, it wouldn't happen. I wonder because I know that they don't normally do it, but what I don't know is if I asked, whether I could get it or not?

PARTICIPANT: No. The only thing that they -- you could get the gender and the age, but not -- and they have to get special permission to even get that.

DR. COX: Okay.

DR. EMANUEL: Wait a second. What about associated -- because all the blood is tested, screened.

PARTICIPANT: Yes, they get the information, all the FDA-required tests.

DR. MIIKE: Well, if it is for research, though, I think that when you check you don't want your blood to be used for actual donations. That may go into the research bank.

DR. MURRAY: Sometimes it is used for research because they have done -- but I don't know how often. I know the Red Cross regions have sometimes done studies comparing rates of infected blood with people, who, in fact, check off "yes" and check off "no." It is the bar code, right.

DR. EISEMAN: I think the information that Jennifer got indicated that pretty much all the blood that the Red Cross gets in goes back for transfusion purposes. So, it is not a huge amount left over. And that is a question that we wanted to try to get a handle on is how much usually do you sell versus how much is used for transfusions.

I think I can safely say the vast majority is used for transfusion. But it would be nice to try to get a handle on how much is used for research.

DR. MURRAY: Among other things, we look at financial statements. I have never even seen that as an item of income. So, my guess is it is trivial.

DR. EISEMAN: Unfortunately, David Corn(?) couldn't be with us today, but he has been asked to

contribute kind of a companion piece that we actually are thinking of combining as one piece because they go so well together with the information I just gave you, which is what is out there, how is it stored, the very nuts and bolts of tissue banking versus what types of research have these tissues been used for and what kind of discoveries have they been used for.

I have just listed a few here. This is not necessarily the ones that are going to end up in the report, but have come from discussions with myself and David Corn, as well as some information from the American Pathology Chairs Survey that was sent out to 80 of the American Pathology Chairs across the United States and about 20 of them responded. So, some of this comes from that as well.

So, here are the types of research that have been aided significantly; obviously, cancer research. That includes the study of all kinds of cancer, cancer research as general as looking at tumor suppressor genes in cancer, all the way to looking at specific cancers, like breast cancer, prostate cancer, HIV/AIDS research, looking for epidemiologic studies, as has been mentioned before; also looking at the causes of Kaposi's sarcoma and the Human Genome Project.

DR. MURRAY: I will say this to David as well. It would be really useful, I think, to have examples of how the more controversial tissue banks, ones with identifiable samples, would they have, in fact -- whether you could have done it without -- you know, done it in a way that people would find less troublesome.

PARTICIPANT: [Comment off microphone.]

DR. MURRAY: That confuses me a little bit because presumably the DES would come from either the woman's statement or the medical record, per se, rather than from a tissue sample collected --

PARTICIPANT: They were seeing unusual cancer. I don't remember whether it was vaginal or cervical --

PARTICIPANT: Yes, it is a cervical cancer.

PARTICIPANT: But they were seeing an unusual kind of cancer and once they put all these cases together and tried to figure out what was causing it, they had to go back to the mothers to find out if they DES during pregnancy. They had to be identified.

DR. EISEMAN: There is also a huge bank in Colorado of samples from the uranium miners to study cancers. So, there are examples. I know David had mentioned specifically the uranium miner example and I will

make sure that --

DR. MURRAY: -- sense of just really what is at stake here in terms of what kind of science might be done.

DR. EISEMAN: The last slide I have is just the research findings that have come out of using stored tissue samples. As I mentioned, the discovery that herpes virus causes Kaposi's sarcoma and proof that it is not caused by HIV, even though that is a common problem that HIV patients get.

The role of Epstein Barr virus in the etiology of lymphomas; the one that is on the top of the news, the BRCA1 mutations in breast cancer and an interesting study of atherosclerosis and heart disease that was done during -- the study used autopsies of soldiers, very young soldiers, who could already see changes in their -- atherosclerotic changes and that was linked to heart disease.

I would be happy to answer any other questions.

DR. COX: So, at the risk of my own peril of bringing this up, there is one full class of stored tissue samples that we need to put on this list. You tell me what it is.

DR. EISEMAN: Yes, sperm. I wasn't clear whether that was something that you wanted to include.

DR. COX: Yes. Sperm, oocytes and embryos.

DR. LO: -- also to explain what proposed test using DNA testing are proposed or planned that couldn't be done without going back to these large -- these stored tissue samples? Not just sort of -- what have we learned in the past, but what are we likely to learn in the future that we wouldn't be able to get at as quickly if we couldn't go back and use these stored samples.

DR. EMANUEL: I think one thing that may be helpful, whenever we sort out, at least, some general idea of what we are going to suggest, to try to understand its impact maybe in some of these cases, would it have barred or made it more difficult, would it have actually prohibited, maybe to put off asking David that just now so we can really hit with all of the questions at once and make it really impossible for him.

But it does seem to me that the bigger question is not so much, you know, which way we go, but how either burdensome or not burdensome is the proposed ideas we are going to have. Now, some of us may have, you know, just from either research we are involved in or research we know about in some sense as to whether that research could go ahead or not go ahead.

But I am sure he also will have a very informed opinion about that.

DR. MIIKE: Are you going to be able to answer that question? I thought the essence of science is the unknowable.

DR. EMANUEL: Well, but there are still some things that you do go to a big -- looking for some associations. Now, you may not find them, but I mean I can think of several studies right off the top of my head that have specifically used stored tissues that, you know, depending on what we decide, either couldn't have gone forward or could go forward.

DR. MIIKE: To me, the question might be sort of a hierarchy of pointers. Some of these kinds of things sort of give you a lead to somewhere else. Was that really a central -- you know, you are going to have a cascade down toward the kinds of more and more pinpointed research.

DR. EMANUEL: Here are ones that come to my mind. Just the breast implant studies that we have had within the last few years, that relied on having those available, you know, just a whole series available. Now, I grant you it is not exactly stored tissue, but anything we say may have impact for those kinds of studies.

Recent studies on breast cancer and proliferation of vessels and things like that, that relied exclusively on stored tissues of breast cancer samples, removed at pathology and then some new studies in the Physician Health Study as we have new ideas about what might cause myocardial infarctions and new tests to predict it, there have been at least two major studies that weren't anticipated when the samples were collected.

So, I think those are the kinds of things -- I mean, I think they are going to be critical for us to know, whether they could have gone or couldn't have gone and they will probably be included in the report.

DR. MURRAY: Yes. And I think this goes to sort of the style of the report. I mean, examples are good and it is my goal to make this report as readable to the non-specialist as possible and I think lost of examples will help me understand it and maybe will help other readers.

DR. LO: Also, I think it goes really to the core of what we are trying to do, is just to balance the perspective for allowing certain types of research to proceed without explicit informed consent versus what we are giving up in terms of confidentiality and privacy and so forth.

Unless we have a clear idea of what at least the speculative potential benefits --

DR. MURRAY: And also what alternatives will be. It may not be a simple tradeoff. It might be that, well, if you do things a little differently, that people still thought was respecting the personhood or whatever, you might actually be able to still do most or almost all of the research that some of us regard as really important.

DR. COX: I would really like to emphasize what Bernie just said because I think people dichotomize it, you know, into all or none, but the parameter that is involved here is simply one of time. That is all that is involved because people say, well, we have got to do it now and other people say, well, why not do it right. So, the dimension is time because you could start prospective study today to find things out in terms of asking questions. People say "no," well, we can't wait and it would be a shame, you know, not to do it now.

So, the time is the really critical parameter and I think that rather than dichotomizing that, you use that time to say, well, how important is the time parameter and what are ways that you can basically respect the person on the one hand and let the other hand be able to get information.

DR. MURRAY: Some questions might be uniquely unanswerable, though. Isn't that true of some of the AIDS -- some of the research on HIV? When did the epidemic begin?

DR. COX: Yes, but I think that the questions that are uniquely unanswerable are very few and far between, very few and far between, because it is an issue of, again, timing because most of the things, you know, still exist. If you want to look at -- again, it is time because we want to look at trends over time. Then that is not an unanswerable, but time is the critical component here.

DR. LO: But it is also resources. I mean, if we have existing samples and I don't have to pay the up front cost of collecting the samples, then I can do certain things, but, you know, if I don't have the funds to do the gathering myself, I can't do --

DR. HANNA: Tom, if you are looking for examples, one thing you might think about doing is contacting one of the PIs, principal investigators, on one of the large prospective longitudinal studies, like the Nurses Health Study or Framingham or whatever, where now they are beginning to -- I mean, there are actually findings coming

out now that are quite useful, based on the ability to go back to samples collected 10, 20 years ago that are linked, and try and find out what kinds of mechanisms they put in place and the protocol as they enroll people, who are otherwise healthy.

I mean, it is a different sample than people that are donating tissues because they are sick. But I think that, to me, it has always been quite surprising that those large prospective studies have seemed to be, at least by appearance, have seemed to have escaped some controversy.

DR. EMANUEL: Well, one of the reasons is they had to have ongoing contact with these people.

DR. HANNA: Right.

DR. COX: And they go back to the people, so the people know up front what they are going to get.

DR. MIIKE: As a matter of fact, as a son of one of the original heart studies, I just got contacted.

DR. MURRAY: It is a valuable suggestion, Kathi. This Physician Health Study, is that a similar --

DR. EMANUEL: Yes. Well, the same few people run all of the physician searches and the health professionals, they are all run by the same three people.

DR. MURRAY: Okay. I think we should go and look at that.

It is after 5:15. It is almost 5:20. We are going to resume at 8:30 in the morning. Are we ready to quit?

We always thank the person who just gave the talk. I am actually tempted to applaud for Elisa. She did, I thought, a heroic job.

[Applause.]

We are adjourned until tomorrow morning.

[Whereupon, at 5:20 p.m., the meeting was recessed, to reconvene at 8:30 a.m., the following morning, Friday, September 19, 1997.]