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Note: Text has been edited for clarity.

Ethics and IACUC Responsibility

Speaker: Dr. Ernest D. Prentice, Ph.D., Associate Vice Chancellor for Academic Affairs, University of Nebraska Medical Center
Moderator: Dr. Jerry Collins, Ph.D., Division of Policy and Education, OLAW and Yale University.
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[It takes several minutes for the recording to load]

Slide 1 (Ethics and IACUC Responsibilities "The Intersection")
Hello everyone and welcome to the OLAW Online IACUC Staff seminar. Today is Thursday June 10th, 2010. I am Jerry Collins and along with Susan Silk, the Director of the Division of Policy and Education in the Office of Laboratory Animal Welfare. I will be moderating today's seminar entitled Ethics and IACUC Responsibilities, "The Intersection." In addition to this seminar for IACUC Staff, OLAW also offers a seminar for Institutional Officials. We encourage you to invite your IO's to join us for that seminar series. Registration information is available on the OLAW webpage at OLAW.nih.gov.

Our audience has grown considerably since the first of these seminars was presented in June of 2008. More than 400 institutions have

registered to participate in today's seminars. We are encouraged by the feedback that we have received from you and continue to encourage you, the participants, to tell your colleagues about this opportunity to enhance their understanding of the challenges associated with maintaining a well-functioning animal program. We will record this IACUC Staff seminar and make the recording available to everyone on the OLAW website in the Education Section. If you have to miss a seminar, or if another time is more convenient for you, you can listen to the recorded version. We will post today's recording as soon as we are able. We will also post a transcript of the seminar and a PDF version of the slides. You'll have to wait several weeks for that, though, since it takes several weeks for us to prepare the transcript. When we upload the recorded seminar, the slides, and the transcript, we also provide a place for you to submit questions. That way if you are listening to it at another time, or if you think of questions after listening to the live broadcast, you may still submit those questions. For today's topic, the website will collect those questions until September 6th 2010. OLAW staff will then work with Dr. Prentice to answer those additional questions. And a document containing both questions and answers will be uploaded to the OALW website. So if you watch the recorded version of the seminar, there will be a way for you to ask questions about the topic. Your interactive participation really enhances this seminar and we appreciate your questions. Throughout the seminar, if you have a question for the speaker, we encourage you to type the question into the 'submit a question' box in the upper left corner of the screen. Only OLAW staff will see what you have written. We will address as many questions as we are able in the time available. [Because you are viewing a recording, you may not submit questions in real time.]

Our speaker today is Dr. Ernest D. Prentice, the Associate Vice Chancellor for Academic Affairs at the University of Nebraska Medical Center (UNMC). He is also Professor of Genetics, Cell Biology and Anatomy and Professor of Public Health. Dr. Prentice is the Executive Chair of the UNMC Institutional Review Board (IRB) and, for over 26 years served as the Co-Chair of the IRB. He also served as IACUC Chair for 12 years and the Institutional Official (IO) for 5 years.

In addition to his scholarly work in the fields of anatomy and medical education, Dr. Prentice is a frequent contributor to the literature on the ethics and regulation of both human and animal research, and he is a frequent speaker at meetings on various aspects of research ethics. He regularly serves as a faculty member for PRIM&R IRB 101/250 courses and IACUC 101/201 courses, which are held at universities across the U.S. Dr. Prentice also serves as a consultant to universities, hospitals and law firms in the private sector, and he is often a member of national panels and writing groups addressing various aspects of research ethics and regulatory oversight of research.

Dr. Prentice is President of the Board of Trustees for the Scientist Center for Animal Welfare (SCAW), Chair of the CITI Executive Advisory Committee, Chair of the ACRP Education Committee, a member of the EPA Human Studies Review Board and the AAAS Committee on Scientific Freedom and Responsibility. He also serves on the Board of Director's for Schulman Associates IRB. From 2003-2007, Dr. Prentice served as the Chair of the Health and Human Services

(HHS) Secretary's Advisory Committee on Human Research Protection (SACHRP).

In 2003, Dr. Prentice was awarded the Harry C. Roswell Award for his contributions to the enhancement of laboratory animal welfare, and in 2005, Dr. Prentice received the Applied Research Ethics National Association (ARENA) Distinguished Service Award. In 2006, the HHS Office of Human Research Protections (OHRP) presented Dr. Prentice with a medallion for Outstanding Achievement in Human Subject Protections.

Today we are honored to have Dr. Prentice here to speak with us about ethics in animal research. Ernie?

Thank you Jerry and I'd like to thank Susan and OLAW for including me in this webinar series and asking me to talk about ethics and the IACUC's Responsibilities. Let me begin with a disclosure. Now, I am not an ethicist or a philosopher. I began my career as a bench scientist utilizing animals and eventually morphed into a research administrator. Some of my colleagues have accused me of going over to the "dark side".

I have, however, thought a great deal about the intersection of science and ethics. I am going to talk about that intersection in relationship to IACUC responsibilities. More specifically, I would like to focus on how the IACUC can apply ethics to protocol review. This, in turn, I think will require a rather philosophical approach.

When we get to the question and answer section, I trust that if there are any ethicists or philosophers listening, you will not invoke Aristotle or Immanuel Kant's perspective on ethical theories, and ask me to go back to college in order to learn what I should have learned the first time around. Please remember, I am an administrator now.

Slide 2 (What is ethics "as applied to research with animals"?)
Let's begin with a question, What is ethics "as applied to research with animals"? The responsibilities of the IACUC, which are articulated in the PHS policy, the Animal Welfare Act, USDA Regulations, and the *Guide*, are grounded in ethics. This, in turn, provides a moral based validation of the federal requirements, which must be met when we use animals for research. It seems reasonable, therefore, to first examine what the term "ethics" means in a broader societal context.

Slide 3 (Ethics defined)
Let's define ethics. Webster defines "Ethics" as a branch of philosophy that seeks to address questions about morality.

Ethics ultimately becomes a question of moral choice – a question of what is morally right and what is morally wrong. While ethics usually reflects societal norms or standards, people can, and often do, have very different views of ethics based upon their life experiences and their personal, cultural, or religious beliefs. Certainly, that is the case with regard to animal research where there are strong opposing opinions concerning what is the correct moral choice.

Slide 4 (Opposing Ethical Based Viewpoints)
As you know, Jerry and our listeners, many people who belong to

animal rights organizations are opposed to animal research on moral grounds. They believe that research using animals is fundamentally wrong and, therefore, unethical. They believe that animals have the right or moral claim not to be experimented upon or exploited in other ways.

As a matter of fact, a recent Gallup poll showed that 34% of Americans surveyed felt that “medical testing” on animals is morally wrong. The figure of 34% may, however, be misleadingly low since the poll did not use the term “medical research” – rather misleading high actually.

On the other hand, biomedical scientists and most of the public at large support animal research, particularly as it relates to the advancement of medicine. They also do not believe that animals have rights or moral claims equivalent to those conferred upon humans. Instead, we have a moral obligation to treat animals humanely and ensure their use is justified. Indeed, that obligation is clearly reflected in the laws, regulations and policies which govern our use of animals in research.

Perhaps at this point, it would be helpful to explore further the concept of a “right”. This is important because the public is often confused about the term “animal rights”.

Once again, let me state for the record that I am also not an attorney or an expert on constitutional law. Therefore, if any lawyers are listening, forgive my lack of expertise because I just am too old to go to law school and the bar is simply too high.

Slide 5 (What is a “right”?)

There are two fundamental or basic kinds of rights. If a right is incorporated into law, it has legal status and is designated as a legal right, such as the right to vote, the right of free speech, and the right of presumed innocence until proven guilty in a court of law.

Rights that do not have confirmed legal status belong to another often misunderstood, nebulous, and contentious category called “moral rights”. These rights are sometimes labeled as “human or universal rights”, referring to their universality of entitlement within the entire human race, regardless of ethnicity. The acceptance of this moral based entitlement has, however, been an elusive goal in many countries.

An example of a moral right would be “the right to liberty and the pursuit of happiness”, which, ironically, is often restricted by law. The freedom to pursue liberty and happiness unabated, obviously, has necessary limitations for the good of society.

Moral rights, like legal rights, are subject to change over time and are culturally dependent within a given society. When a moral right gains widespread acceptance within a given society, it becomes validated and may then evolve into a legal right, thereby acquiring the force and power of law. This is how laws usually evolve.

People who ascribe rights to animals are, in the absence of supporting legal adjudication, really referring to “moral rights”. In accordance with the concept of a moral right, one can and should argue that animals

have a fundamental “moral right” to be treated humanely in research and, indeed, in all other areas where they are used.

Slide 6 (What does “humane” mean?)
Let us now explore the word “humane”. According to Webster, the word “humane” means having the “good qualities of kindness, mercy, and compassion”.

An animal activist would likely argue that any use of an animal in painful research, if not all animal research, is *á priori* “inhumane”.

A biomedical scientist, however, would undoubtedly have a different interpretive application of the term “humane”. He or she would believe that animal research is necessary for the “human or animal good” and that animals should be treated with as much kindness, mercy, and compassion as possible within the limitations imposed by legitimate scientific needs. In other words, animals should be treated as “humanely as possible” when they must be used in research, and are subjected to any necessary pain or discomfort associated with the research.

Slide 7 (no title – pictures of the PHS Policy, the *Guide for the Care and Use of Laboratory Animals* and the Animal Welfare Act and Animal Welfare Regulations)
As mentioned previously, the PHS Policy, the Animal Welfare Act, USDA Regulations, and the *Guide* are grounded in ethics and set standards for the humane care and use of animals in research, testing, and teaching.

Let us now focus on the term “care and use”. “Care” obviously implies how animals are cared for in the research setting. As every IACUC knows, standards must be met concerning food, water, housing, husbandry, and veterinary care. It is the responsibility of the IACUC to ensure that these standards are met.

The word “use” means how the animals would be used in the project. It is also the responsibility of the IACUC to ensure that the use of animals is justified. Indeed, if animal use is not justified, it is *á priori* unethical to use the animals in the project.

Good research, which should be the goal of all investigators and their institutions, clearly goes hand in hand with good ethics. Research projects must have sufficient scientific merit that justify the use of the animals. So let’s now examine the term “scientific merit”.

Slide 8 (“Scientific Merit”)
Webster defines “merit” as having the “state of worth, value or excellence.” When the noun “merit” is combined with the adjective “scientific”, it means “of scientific worth, value or scientific excellence.”

Slide 9 (More on Scientific Merit)
Moving beyond Webster, which is basically a laymen's dictionary, let us dissect the term “scientific merit” using this quote from an article written by Gordon.

According to Gordon, “In order for research to have scientific merit, the research should be based on a significant hypothesis and, if possible, oriented towards uncovering an important biological

mechanism. The hypothesis should be testable…by the proposed experiment."

No responsible scientist would disagree with the imperative that research involving animals must have sufficient "scientific merit" to justify the use of the animals. There is, however, persistent, but understandable, confusion about the IACUC's role in scientific merit review.

Slide 10 (PHS Policy on "Scientific Merit")
Indeed, this has been a contentious issue ever since the PHS Policy became effective in 1986. So, let's now "dissect" the PHS Policy by examining those sections of the policy which either directly or indirectly address the IACUC's responsibility for scientific merit review.

Slide 11 (PHS Policy on "Scientific Merit")
The PHS Policy requires compliance with the nine U.S. Government Principles, and the acronym you see on this slide is USGP. These principles are titled the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Teaching. The PHS Policy also requires assured institutions to base their programs of animal care and use on the *Guide*.

U.S. Government Principle II is undoubtedly the most relevant and important requirement which addresses "scientific merit". In accordance with U.S. Government Principle II, when an IACUC approves a research protocol, the committee must be assured that the research has "relevance" – "relevance" – to human or animal health,

advancement of knowledge, or the good of society. “Relevance” means the research is “pertinent”.

The *Guide* requires the IACUC to ensure there is no unnecessary duplication, which, as you know if it existed, would compromise the value of the research and waste animals.

U.S. Government Principle III addresses the need to use procedures and the appropriate species necessary to obtain “valid results”.

Slide 12 (PHS Policy on “Scientific Merit” cont’d)
To continue, U.S. Government Principle III also addresses the minimization of animal numbers in consideration of the need to obtain valid results and the PHS policy at section IV.C.I.a. refers to “sound research design”.

Slide 13 (PHS Policy on “Scientific Merit” cont’d)
Note that in this slide, the PHS Policy refers to “scientifically valuable research” and U.S. Government Principle IV mentions “sound scientific practices”.

Slide 14 (PHS Policy on “Scientific Merit” cont’d)
The PHS Policy addresses the withholding of pain relieving agents only if it is justified for “scientific reasons”. Finally, note the requirement that personnel who conduct research on animals must be “appropriately qualified and trained”.

Slide 15 (“Scientific Merit" – diagram)
If we combine all of the terms in the PHS Policy and the *Guide* which

appear to reflect “scientific merit,” I think it is clear that the IACUC cannot ignore the science or the potential merit of the research.

For the purpose of achieving greater clarity, let me engage in some “literary synthesis”. Before an IACUC approves a research protocol, it should find the following:

1. The research has a sound research design and will employ sound scientific practices.
2. The research will yield scientifically valid results which are not unnecessarily duplicative.
3. The research has relevance to human or animal health, the advancement of knowledge, or the good of society.
4. The research is scientifically valuable.

In other words, when the committee approves a research protocol, there must be sufficient “scientific merit” to justify the use of the animals. I would contend that this represents a major obligation of the IACUC.

Slide 16 (OPRR (OLAW) on “Scientific Merit”)
Given how contentious the issue of scientific merit review by the IACUC has been, it proved very helpful when the Animal Welfare Division of OPRR provided guidance in 1991. OPRR is the acronym for the Office for Protection from Research Risks. In June 2000, the Animal Welfare Division of OPRR morphed into OLAW.

According to OLAW guidance, “The primary focus of the IRG, which is now called the Scientific Review Group, is scientific merit, whereas the

primary focus of the IACUC is animal welfare. It is evident, however, that there is overlap of function between the two bodies. The IACUC is expected to consider in its review, the general scientific relevance of the proposal."

Note the term "general scientific relevance". This term obviously reflects U.S. Government Principle II which, as mentioned previously, refers to the relevance of the research to human or animal health, the advancement of knowledge, or the good of society. As I mentioned earlier, U.S. Government Principle II is perhaps the most important principle which addresses both the scientific and ethical justification for the use of animals in research.

Slide 17 (Can the IACUC defer…?)
This is a question that is often asked. Can the IACUC defer the assessment of the potential relevance and scientific value or merit of the research to other peer review bodies?

Slide 18 (The IACUC Can't Pass the Buck!)
The answer: The IACUC can't pass the buck! The IACUC cannot defer the assessment of scientific merit to other review bodies. Certainly, if valid "scientific merit" review takes places before IACUC review, the committee can be reassured that another expert body has carefully examined the science of the project. This does not, however, negate the IACUC's obligation to ensure compliance with the PHS Policy. Accordingly, NIH peer review cannot and does not supersede IACUC review. This issue was addressed in the August 2002, revision of the PHS Policy. [PHS Policy IV.C.8]

Slide 19 (The PHS Policy)
As you can see from the quote on this slide from the revised PHS Policy, in no way is [NIH] peer review intended to supersede or serve as a replacement for IACUC approval.

Slide 20 (Ethical Cost Benefit Assessment)
Now that we have discussed the IACUC's responsibility to review the science, let us consider what I believe to be the cardinal responsibility of the IACUC. It's the ethical cost-benefit assessment of the research. An acceptable ethical cost-benefit relationship ensures that the research as proposed is ethical.

Slide 21 (Ethical Costs)
The ethical costs of research using animals are pain, discomfort, distress, morbidity, and mortality. These ethical costs are both procedure-specific and animal-specific. The ethical costs may increase or decrease depending on the nature and invasiveness of the procedure or intervention, and on how sentient the selected animal subject is.

Once again, using Webster's, "sentient" is defined as "being responsive to, or conscious of, sensory impressions". For example, both a nonhuman primate and a mouse are capable of feeling pain, but since the nonhuman primate is more sentient, the degree to which the nonhuman primate has a conscious response to the painful procedure is considerably more complex. As such, this represents a higher level of cognition and animal awareness than we attribute to a mouse undergoing the same procedure.

The ethical differences in the use of an animal based upon sentience can be expressed in four guiding ethical principles that can help the IACUC in judging whether the ethical costs of the research are justified. These ethical principles are clearly in keeping with the 3R's and the U.S. Government Principles which I mentioned earlier.

Slide 22 (Principle I)

Principle I. Using an intervention applied to a less sentient animal subject that causes the least possible pain, discomfort, distress, morbidity, and mortality reduces the ethical costs of the research. I think most folks would agree that they have less ethical concern about using a zebra fish for research purposes than a mouse or a rat.

The ethical concern, however, escalates when the animal subject is a higher order species, such as a dog, a cat, or a nonhuman primate. Indeed, this is a reflection of what is called "speciesism". This occurs when an animal's moral status is a determinant in how, when, and if they will be used. Generally speaking, a higher order species is assigned a higher moral status.

As a matter of fact, "speciesism" is ultimately the fundamental justification for our use of animals in research. The vast majority of research animals are used in an attempt to advance science and medicine for the benefit of we humans who belong to the genus *Homo sapiens*. This is because most people who belong to the human race think humans have a higher moral status or worth than animals.

Slide 23 (Principle II)

Principle II. The same intervention which causes pain, discomfort, distress, morbidity, and mortality, applied to a more sentient animal versus a less sentient animal increases the ethical costs of the research. As mentioned previously, this is because a more sentient animal is capable of a more complex conscience response to the adverse effects associated with the research interventions.

Slide 24 (Principle III)
Principle III. The greater the scientific value of the research, the higher the level of pain, discomfort, distress, morbidity, and mortality that is acceptable, i.e. the ethical costs.

For example, assuming that an infectious disease study using animals has significant scientific value in terms of the advancement of human or animal health, the magnitude of the ethical costs which become acceptable are greater, but there are, of course, limits to acceptability.

There were many important studies conducted prior to the 1985 amendment of the Animal Welfare Act that would likely not be approved by today's IACUC because the ethical costs are simply too high.

Slide 25 (Principle IV)
Principle IV. Investigators and the IACUC should strive to achieve the most favorable ethical cost-benefit relationship possible which means the ethical costs of the research are as low as possible, and the potential scientific value of the research clearly outweighs the ethical costs. This principle reflects the ethical importance of diligently applying the 3R's when possible within valid scientific constraints.

Slide 26 (Ethical Cost-Benefit Relationship)
This slide shows an acceptable ethical cost-benefit relationship using a scale for illustration purposes. The IACUC has determined that the research has potential scientific value to humans, or to animals, or to science, or to society. In addition, the IACUC has decided that the potential scientific value is, in turn, balanced by the ethical cost of the research which may be pain, discomfort, distress, morbidity, or mortality. This means, the research as proposed is ethical.

Now, the greater the potential scientific value, and the less the ethical cost, the more favorable the ethical-cost benefit relationship becomes. IACUCs should strive to help investigators achieve the most favorable ethical-cost benefit relationship possible. IACUCs should view themselves as the investigator's partner in the ethical decision-making process.

I am sure you all recognize that there is no computer software which the IACUC can use to perform this assessment. Instead, it requires the thoughtful judgment of the men and women who serve on the IACUC. During protocol review, the members of the IACUC should bring to the table their expertise, experience, value judgments, and moral beliefs, recognizing that the committee is acting as society's gatekeeper. Society expects the IACUC to ensure that research involving animals is, indeed, ethical.

Slide 27 (Our Obligation)

Finally, let me end by reminding all of us in science of our obligation. When we use any animal in research, be it rodent or nonhuman primate, we must do so with compassion, humility, sound ethics, and humaneness. Once again, good science goes hand in hand with good ethics. Thank You.

Thank you, Dr. Prentice for your very thought-provoking comments. We will spend the remainder of our allotted time responding to questions that we have received from you, the participants, and we will begin with some questions that were submitted prior to this webinar.

Ernie, the first question is, **Are there any formal statements about society's view of animal use being moral?** Well, thank you for that question Jerry. As a matter of fact, I referred to the Gallup poll actually that was conducted in the month of May of this year, and that Gallup poll showed 59% of Americans surveyed felt that medical testing on animals was morally acceptable and that figure is pretty consistent, actually, over the years when these polls have been conducted. But I'd like to go back further in history, in 1947 the Nuremburg Code was issued as a consequence of the Nazi Doctor's Trial where 20 physicians where tried for crimes against humanity. Arising out of that trial came the Nuremburg Code. One of the principles of the Nuremburg code requires medical experimentation prior to the utilization of humans. The 1964 Declaration of Helsinki has a similar principle which requires appropriate animal experimentation before humans. So I think that these principles demonstrate that it is considered moral and ethical to utilize animals in research for the benefit of humans.

Our next question, **In several of your slides you mention the 3R's. What are they and how should they be applied?** Well, the 3R's arose from a book, written by Russell and Burch issued in 1959. The interesting thing about the 3R's before I describe them is the fact that from 1959 until about 1985, there was not much attention paid to the 3R's. However with the 1985 amendment of the Animal Welfare Act, the revision of the Public Health Service Policy and of course subsequent editions of the *Guide*, we're seeing the 3R's reflected in the federal requirements which govern our use of animals in research. But to go back to the 3R's, the 3R's are replacement, refinement, and reduction. And, I'd like to refer you actually to a prepublication copy of the new *Guide*, which has a very concise description of the 3R's [page 4]. Replacement refers to methods that avoid using animals, so the term includes an absolute replacement, i.e. replacing animals with inanimate systems, such as computer programs, as well as a relative replacement which means replacing animals such as vertebrates with animals that are lower on the phylogenetic scale. I would suggest that this speaks to that principle of sentience that I talked about earlier. Refinement refers to modifications of husbandry or experimental procedures to enhance animal wellbeing and minimize or eliminate pain and distress. Reduction includes strategies for obtaining comparable levels of information from the use of fewer animals or for maximizing the level of information obtained from any given number of animals without increasing pain or distress. So, in the long run, fewer animals are needed to acquire the same scientific information. So clearly, the new edition of the *Guide* is certainly endorsing the 3R's as being extremely important.

Another question relating to the 3R's, from an ethical standpoint, is there one of the 3R's that is most important? Well, that's a really challenging question. I believe that the overwhelming majority of people, including scientists, look forward to the day when we no longer need to use animals in research, particularly painful research. Unfortunately, that day is not going to come in my lifetime. Nevertheless, I think you would agree Jerry, that remarkable progress has been made in the development and use of alternatives by the research community. So from an idealistic viewpoint, I think that replacement is the most important R. However from a pragmatic viewpoint, since we have to use animals in research to further advance science and medicine, I would have to say that refinement trumps replacement.

Ernie, near the end of your presentation you listed four principles that you enumerated, how do they relate to the US government principles? Well, Jerry, as you know, I've been involved with IACUCs for a very long time and I have obviously read the U.S. Government Principles many, many times and I've written papers that have incorporated the U.S. Government Principles and I've certainly read Russell and Burch's book on the 3R's. So I've thought a lot about how I could sort of take these principles, take the 3R's, take some of the requirements in the USDA Regulations and the *Guide* and sort of develop a set [inaudible]. And, certainly, Principle II is featured prominently, Principle II, as you recall, procedures involving animals should be designed to perform with due consideration of their relevance to human or animal health, advancement of knowledge, or the good of society. If we look at Principle III, that is reflected in the

need to consider replacement of live animals and less sentient animals.

So we could appropriately refer to these then as Prentice's Principles?

You know, I'd love for you to do that Jerry but I don't think I could take credit. [inaudible]

[It seems that your suggested ethical cost benefit analysis is actually a two-step process. The first is focused on being sure that the science is justified. Once that has been done, the next task is to ensuring humane care. In the real world how does an IACUC, working with an investigator, complete these tasks?] Okay, as you know Jerry, I do operate in the real world. And, as I said, I'm not a philosopher or an ethicist so I try to think of these requirements in a pragmatic way. [inaudible] Eventually, and on an ongoing basis, because you know, research ethics evolves and our interpretation of the PHS Policy and USDA Regulations has also evolved considerably. Number four, perform thorough comprehensive IACUC reviews. Number five, develop IAUCUC review letters that are explanatory and educational in nature. I've unfortunately seen too many IACUC letters that are terse, do not really contain an adequate explanation concerning what the IACUC is asking for, whether it would be a clarification or a modification. I really believe that we can utilize review letters to further enhance the education of our investigators. Number six, treat investigators as the IACUC's customers. I really believe that we need to facilitate communication between IACUCs and our investigators. And number seven, perform post-approval monitoring on a diplomatic, educational and facilitatory basis.

Next question, **If ethical means justified and humane what expertise does an ethicist bring to the discussion and do you believe that all IACUC's should include an ethicist?** Well, that's another interesting question. The ethicists that I know and like are all philosophers, that seems to be part of being an ethicist. I would characterize them as deep thinkers. They are able to ask penetrating questions, formulate concepts that I would never think of. I believe that inclusion of an ethicist on the IACUC brings value to the committee's reviews. A good ethicist who is knowledgeable about animal research issues and one who can strike a balance between ethical-based idealism, shall we say, and the realities of scientific inquiry in our laboratories is really a good addition to an IACUC.

Okay, another question about the 3R's, **Reduction is one of the 3R's. How do you balance reduction with the reuse of animals?** That's another challenging question. And, really, actually, that's a thorny ethical question. The new *Guide* that I referred to earlier does not advocate animal reduction as a reduction strategy – you mean animal reuse as a reduction strategy – I'm sorry – yes, I guess you've read the *Guide* more than I have. Thank you for that correction – particularly when experiments involve severe, chronic pain. I believe that investigators in IACUCs should consider the quality of life of the animals when considering, shall we say, reusing or recycling. There's a common saying that you're very familial with 'Enough is enough'. In an ideal world, I think it would be wonderful, if for example, nonhuman primates, dogs, and other high order species that did not have to be euthanized for scientific reasons could be retired, sort of like you and I retire, after serving humanity as an animal research subject. Indeed,

some institutions have adoption policies that allow certain research animals, like dogs, to be adopted if they are found fit for adoption.

Ernie, I'm going to repeat that question. It could be that the sound quality which is not up to the standard that we would want to have didn't allow all of the question to get through to the listeners. So the answer that you just gave is the answer to the following question. Reduction is one of the 3R's. How do you balance reduction with the reuse of animals?

Moving on to the next question, **In your opinion, is there one document that has done the most to improve the ethical use of animals in research?** Well, I have to say that, I believe the U.S. Government Principles is perhaps the most important ethical document that I could use to answer your question. I believe that if all investigators religiously understood and followed the U.S. Government Principles for the Utilization [and Care of Vertebrate Animals Used in Testing, Research, and Training…inaudible].

From an ethical perspective why is it OK to exterminate a mouse, a vermin, when it is your home, but when a mouse is used in research, there are stringent standards that must be met to ensure their humane treatment? Well, when a mouse become a surrogate for a human in research which basically means that they are substituting for us humans we are introducing cancer, introducing infectious diseases, creating various clinical conditions, in the hopes that we're going to find better and more effective treatments, that mouse achieves a higher moral status, if you will.

Their moral status is elevated and so is our moral obligation to treat that animal humanely. Under the auspices of [inaudible] IACUCs.

Next question, **How should an IACUC judge the scientific merit of a protocol?** Another very good question, let me give you a number of points that I'd like our audience to consider. First, if the IACUC does not have sufficient expertise to review the science of the research proposal, I think they need to use consultants. In my view, IACUCs don't use consultants enough. Secondly, and I referred to this earlier, ask the right questions on your protocol review form. For example, ask the PI to address the aims and objectives of the project. The potential scientific value of the project, ask the PI to describe the experimental design, the groups, the number of animals per group, the scientific and/or statistical justification for the number of animals in the groups and the qualifications and expertise of the investigator. I think that these are examples of crucial questions that should be asked that will help enable the IACUC to look at the science in a valid way.

The next question has a bit of a preamble associated with it. **My question is nothing new, and is a bit more broad than just the IACUC's responsibilities. Regulations cannot drive ethics. I see many brilliant researchers who sincerely want to do the right thing, but who are burning out under the increasing burden of regulations. How can we achieve the balance of supporting an ethical environment but not crush the invaluable research going on in our institutions?** That's a common expression of concern, I hear it all the time from my investigators, I am very, very sympathetic. I'm very concerned about striking the right balance between insuring that regulations are followed but not over interpreting regulations unnecessarily and creating undue regulatory burden. I would like to think that

institutions, (one) resource their IACUCs adequately, (two) provide an appropriate research infrastructure to support the activities of their researchers. (Three) I believe that institutions should seek to promote and foster a culture of compliance and conscience where pretty much everybody does the right thing because it's the right thing to do not because we have regulations or the PHS Policy but simply because this is what we should be doing. If ethics means making the right judgments, doing the right thing, then I think we would not find that ethics is at odds with the pursuit of science and creating undue regulatory burden.

Okay, and our final question, **Principle II seems questionable. P&D (pain and distress) is pain and distress. How do the observably more complex reactions in "more sentient" animals prove reduction or increase of ethical cost to the animal in question? Having said that, I believe your balance between the scientific value versus ethical cost is right on.** Well, I want to empathize the fact that pain indeed is pain. Certainly, there is no provision in the PHS Policy, USDA Regulations, or the *Guide* to discriminate based upon species concerning the relief of pain. All pain must be minimized no matter what species or animal is used in the research. However, I'm not a behaviorist but it would seem to me that the more sentient an animal is, and we can go all the way up to the human being, they have the capability of reacting to pain including psychological ramifications whereas a lower order species does not necessarily have that capability, although I am certainly not minimizing the importance of the pain in that animal and the need to relieve that pain.

Well that's it for the questions. Dr. Prentice, I want to thank you on behalf of all of our participants for taking the time to share with us your very thoughtful comments, and clearly comments based upon years of deliberating about these very challenging issues. Thank you to all the participants for joining us, we look forward to your joining us for future sessions. We hope that you will send your comments and suggestions about this and future seminars to the OLAW e-mail box which can be found at the bottom of the OLAW webpage. [http://olaw.nih.gov]

[inaudible]

[The September webinar will provide an opportunity for a discussion of revisions to the *Guide for the Care and Use of Laboratory Animals*. A prepublication copy of the 8th edition of the *Guide* has been issued by the Institute for Laboratory Animal Research of the National Academy of Sciences and is available on their website. Please note, however, that the 1995 edition of the *Guide* remains in effect. OLAW will issue guidance on the implementation of the 8th edition of the *Guide* after it is published.]

Once again, thanks for listening and hope you have a good summer. Goodbye.