DO CURRENT FEDERAL REGULATIONS ADEQUATELY PROTECT PEOPLE WHO PARTICIPATE IN MEDICAL RESEARCH?

HEARING

BEFORE THE

SUBCOMMITTEE ON CRIMINAL JUSTICE, DRUG POLICY, AND HUMAN RESOURCES

OF THE

COMMITTEE ON GOVERNMENT REFORM

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DO CURRENT FEDERAL REGULATIONS ADEQUATELY PROTECT PEOPLE WHO PARTICIPATE IN MEDICAL RESEARCH?

THURSDAY, DECEMBER 9, 1999

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON CRIMINAL JUSTICE, DRUG POLICY,
AND HUMAN RESOURCES,
COMMITTEE ON GOVERNMENT REFORM,
New York, NY.

The subcommittee met, pursuant to notice, at 10:38 a.m., in the Auditorium of the New York County Lawyers Association, 14 Vessey Street, New York, New York, Hon. John L. Mica (chairman of the subcommittee) presiding.

Present: Representatives Mica and Towns.

Staff present: Sharon Pinkerton, staff director and chief counsel; Steve Dillingham, special counsel; and Lisa Wandler, clerk.

Mr. MICA. Good morning, I'd like to call to order the Subcommittee on Criminal Justice, Drug Policy, and Human Resources of the U.S. House of Representatives. We're pleased to be in New York City this morning for this field hearing, and I want to first extend my appreciation to our subcommittee member, Mr. Towns, who I've had the honor of working with in Congress since I came in 1993, and the previous chair of one of the subcommittees. We've worked together over the last four terms on issues of usual concern and I appreciate your persistence in the issues before us today and also the leadership that he has provided us both on this issue and on other matters we've worked together with in the Congress.

I thank you for hosting us today, and we will proceed. I will proceed in this fashion. I will start with an opening statement. I'll recognize Mr. Towns. Then we will proceed to our panels, and there are two panels today, of witnesses.

Today's hearing before the Subcommittee on Criminal Justice, Drug Policy, and Human Resources, will examine an issue of great importance and tremendous complexity. The issue before us today is whether Federal regulations offer adequate protection to participants in medical research, a topic that probably couldn't be more timely.

In recent weeks, considerable national attention has been devoted to the tragic death of 18 year old Jessie Gelsinger of Tucson, AZ. He died in September as a result of a gene therapy experiment. Jessie died 4 days after being injected with a modified cold virus, and engineered genes into an artery leading to his liver. Research-

ers were shocked by his death and have not determined exactly why he died.

The case has stirred a national debate on gene therapy experiments and the reporting of its adverse affects. It also prompted the National Institutes of Health to issue a solicitation to the medical community requesting related help.

I noticed today in reading this morning's edition of the New York Times, Mr. Towns and others, FDA officials, I guess yesterday have come up with some disclosures on what took place with this case, and it said, let me just cite for the record,

> Officials of the Food and Drug Administration said today Jessie Gelsinger, an 18 year old Arizona man who lost his life in a gene therapy experiment in September was ineligible for the clinical trial and should not have been treated because his liver was not functioning well enough before doctors infused him with a dose of corrective genes. In announcing the preliminary results of their inquiry of Mr. Gelsinger's death, officials also said the University of Pennsylvania scientists running this has violated FDA requirements by failing to report immediately information about two patients long before the death who had experienced serious side effects and had said the informed consent form the investigators gave patients deviated from the one the agency had approved.

I thought that was interesting and timely, given the subject before us today. NIH is now calling on researchers to report ill effects from experiments of this type. It appears, as this article points out, the previous deaths have occurred from experimental research that had not been reported to NIH. Accordingly, Federal regulatory changes have been proposed.

The example of gene research illustrates a question before us today. What further Federal regulations are needed to reduce unnecessary health and safety risks to human subjects? I will keep an open mind throughout this hearing, but I do think there is a growing concern that current Federal regulations do not offer the full range of protections that many would like to see. This is true despite the fact that many Members of Congress, including myself, are often very skeptical of increasing government regulations, particularly Federal regulations imposed on business and private activities.

I'd also add, one of the things that we do not want to do is to hamper legitimate research in any way, or deter legitimate research and basic fundamental human research, which is so important.

Our focus today, however, is on research and institutions that receive Federal money. Our subcommittee has oversight responsibility to insure that such research is conducted both properly and safely. A key topic in this discussion is the critical roles played by institutional review boards, commonly referred to as IRBs. These IRBs oversee human subject research. IRBs are required to protect human subjects participating in federally funded research projects.

IRBs are governed by common Federal regulations adopted by 17 agencies that are engaged in human subject research. IRBs typically review and approve research plans before research is carried out. This review includes research protocol, the informed consent document to be signed by the subjects, and advertisements to be used in recruiting subjects.

In carrying out this review, the IRBs seem to insure that potential risks are warranted and reasonable in relation to potential

benefits. IRBs insure that informed consent documents clearly identify known risks and the true nature of the research being conducted. This includes guarding against advertisements that might be misleading and selection procedures that might be biased or unfair.

The responsibilities of IRBs do not stop once the research has begun. They're required to exercise continued oversight of research studies involving human subjects. Such oversight includes examining reports of adverse incidents involving research subjects and also requests for changes in the research methodology.

The Federal department that has the greatest role in overseeing human subject research is the Department of Health and Human Services. Within HHS, the Food and Drug Administration [FDA], and the Office of Protection from Research Risk [OPRR], are the two agencies with primary responsibilities for overseeing activities and also for implementing human research subject regulations and protections.

In studies involving biomedical research, the FDA monitors the safety of human subjects through its Center for Drug Evaluation and Research, also known by the CDER designation.

The Office of Protection from Research Risk [OPRR], has the critical responsibility of implementing basic HHS policy for protecting human research subjects in HHS research and also overseeing the IRBs.

HHS annually invests approximately $5 billion of its research dollars in approximately 16,000 research projects that involve human subjects. To provide oversight for these research projects, OPRR has agreements with more than 4,000 federally funded institutions to insure and protect the human subjects that are involved. Each institution that receives funding must establish an IRB. IRBs are typically made up of scientists, doctors and patient representatives to monitor and enforce ethical research standards. Federal regulations require that a non-scientist and an individual not affiliated with the institution be included in each of the IRB panels.

Under OPRR guidelines, all potential research subjects must be fully briefed on the purpose, duration and procedures of a research project before agreeing to participate. OPRR has the authority to investigate and require corrective action or suspend funding to an institution until problems are resolved.

For example, there was much publicity this year when OPRR temporarily suspended Duke University research funds because of Federal compliance concerns. Obviously, with so many departments and agencies involved, so many research protocols to enforce, so many projects to monitor, so many dollars invested, and so many human subjects at potential risk, the complicated task of insuring an adequate level of protection from avoidable risk, or even abuse, can become somewhat overwhelming.

As we will hear today, there is significant concern that OPRR has been overwhelmed in the past and that reforms may be needed. This was the conclusion of the HHS Office of Inspector General in a report that they issued.

Today we'll hear that some changes are underway in response to these concerns. For example, Secretary Shalala recently announced

the relocation of OPRR from NIH. OPRR will now report to her office and leave the regulation of animal research within NIH.

But are these minor changes enough? If not, what additional changes are needed? Furthermore, shouldn't we have a clear accounting of the 3,000 to 5,000 estimated IRBs that are bound and required to implement Federal standards? If we aren't sure of the number of IRBs, and how to contact them, how can an OPRR, FDA or anyone else adequately monitor their activities and their capabilities?

In considering reforms, there are a number of specific concerns that I feel merit our closest attention. Foremost among these is the need to protect against conflicts of interest that might result in increased risk of research participants and others who may be impacted from the research. I read recent accounts, situations even here in New York, where IRB members may have received money and funds from pharmaceutical companies with a financial interest in research projects that they oversee. Pharmaceutical research, of course, can have enormous financial consequences.

Doesn't this present a serious potential conflict that can influence research decisions and judgments? Is the mere disclosure of financial interest enough to assure scientific and medical objectivity? I'm concerned that while this subcommittee and HHS, Office of Inspector General have previously identified some of these problems, and have put forth some valuable solutions and recommendations, it appears that none of these solutions have been implemented to date.

Why not? We'll also review today if legislative action or administrative additional action is necessary.

Human subject research is an issue that is national in scope and deserves attention at all levels of government. Today's hearing hopefully will increase our understanding of what additional improvements and protections may be needed. We'll have with us today a number of distinguished government officials, medical researchers, and others who are knowledgeable and experienced with research involving human subjects. We appreciate their willingness to appear before the subcommittee to share both their knowledge and experience with us. We look forward to their insight, to their recommendations and also for their update on the progress that's being made with the recommendations that have been made in the past.

I'm pleased at this time to yield to Mr. Towns, a member of our subcommittee, and as I said, Mr. Towns has pursued this matter for some time. I believe this is the third Federal congressional hearing on this matter, and his persistence has brought both attention and some reform that is needed, and we anticipate this hearing will result in some additional changes in procedures, but I thank him for his participation and for his leadership on this issue, I'm pleased at this time now to yield to the gentleman from New York, Mr. Towns.

Mr. TOWNS. Thank you very much, Mr. Chairman. Let me also add that I really appreciate you taking the time from your busy schedule to come to New York to have this hearing. Also, it's been a pleasure to work with you on this issue and also other issues

over the past 8 or 9 years, so I want to let you know I appreciate that as well.

I want to take this opportunity to thank all of you for coming, especially those from Washington, DC, Albany, NY, and places near and far, to attend this hearing, and I want to thank the New York County Lawyers for providing space for us to have this hearing.

Mr. Chairman, medical research on human subjects knowingly subjects some individuals to potential harm to seek benefits for a greater number of people. Federal regulations are intended to provide guidelines that protect the individual without reasonably hampering research goals. Under Federal regulations, research could only proceed if the research subject provides a valid, informed consent, has a capacity to understand the information, the ability to weigh the advantages and disadvantages of pursuing the research and access the benefit and risk of the drug or procedure. Yet numerous cases have been in the press lately, where this has not been the case, so it's so important for us to consider that and take a look at where we are today.

In light of the risk and dangers posed by these types of experiments, we must seriously consider legislation that will make the IRBs fully independent of research institutions; that will assure that research methods meets customary standards of scientific excellence that will assure that children and parents are fully informed about the real purpose and intent of the research; that will permit them to decline or refuse to participate without fear of retaliation, and that will subject research programs that confer no benefits on the subject or that result in stigmatization of racial groups.

Mr. Chairman, again, I want to thank you for taking the time out, and I say to you that we've had some success already, but we hope to be able to have some more, because I am also concerned about the fact that these independent review boards, IRBs, we don't even know how many are out there. We don't even know whether there are qualifications for them, we don't know that. The point is that it also has potential for all kinds of conflict, and if you don't know how many are out there, how can you regulate them? I think that's also a real concern, but also, I can't help but think about those experiments that took place in the time of the Tuskegee experiment, I can't help but think about that, and many, many others. Of course you referred to one in the Washington Post, so a lot of things are going on, and I think we can no longer close our eyes. We have to come to grips with this and begin to deal with it because we're talking about human beings. I think that's very, very important.

And the last thing, Mr. Chairman, that, you know, I'm getting reports coming from various sources that people are being encouraged to participate in research groups and reported that many times they're given, like, toys, or being paid a few dollars to be in it, and they don't even know the danger or the risk that's involved, and that really bothers me as well, so I'm hoping that we can sort of come up with some guidelines and have some legislation, of course, that I think that will correct that, but my point is I think that through this hearing process maybe we can get a better han-

dle on this. Because to have these review boards out there, and we don't even know how many that exist, there's no qualifications in terms of people on them, so you pick your friends, your buddies, that just to me should not be in the United States of America.

So Mr. Chairman, here again, I thank you so much for coming to New York and having this hearing.

Also, we've had some success, as I indicated early on. We have a letter from the Office of Surgeon General David Satcher and we have a note, I think I'll just read this paragraph, Mr. Chairman, before we go forward.

It says,

> Moreover, we believe that no federally supported research should be compromised by any selection of human subjects that is not supportable by clear and advised scientific explanations. To this end, I will convene a group comprised of knowledgeable individuals who have not been associated with the investigation to examine the process and the context of the regulations, make recommendations, and to provide me with a summary report. I will contact you with the results upon completion.

Then it goes on to say he will get back.

> The Department has not previously issued guidelines on these terms and the context of regulations and I agree that the terms need clarification. An essential element in the Secretary's decision to relocate human subject protection component of OPRR is the formation of an independent advisory body organized under the Federal Advisory Committee Act to provide guidance, assist in setting standards, review the operations of the new office and address human subjects' protection in general. This advisory committee will be known as National Advisory Council on Human Research and Protection, NACHRP.
>
> I believe the best approach to the development of a clarification of the term is for the question to be addressed by the council. In this way, multiple interests and views can be considered and methodology examined, thus providing a solution for acceptable regulatory clarification that protects both human subjects and does not necessarily impinge on the advancement of science. I will bring this issue to the council for their attention as one of the first matters of priority business.

Mr. Chairman, I think that's a step in the right direction. I wish I could say it's a giant step. It's not a giant step, but it's a step in the right direction. So thank you so much for having this hearing today. Let me say this of note. It says—well, actually let me now yield.

Mr. MICA. Mr. Towns, if you want that part of the record?

Mr. TOWNS. Also, Mr. Chairman, may I add, that I'd like to put my entire statement in the record.

Mr. MICA. Without objection, the entire statement, letter from the Surgeon General Satcher will be made part of the record.

Mr. Towns, if it's appropriate, we will leave the record of this hearing open for 3 weeks for statements of Members who haven't been able to attend, and also the hearing may generate additional questions of these and other witnesses.

Without objection, so ordered.

We'll proceed now, and let me say at the outset that this is an investigations and oversight subcommittee of Congress. We have a broad range of authority and responsibility. We do swear in our witnesses, which I'll do in just a minute.

I will introduce the first panel, and we have two panels today. The first panel consists of Dr. Arthur J. Lawrence, who is the Deputy Assistant Secretary for Health, Office of Public Health and Science in the U.S. Department of Health and Human Services.

Some of you have accompanying witnesses. Dr. Lawrence, do you have anyone with you?

Dr. LAWRENCE. Yes, sir, Dr. Ellis.

Mr. MICA. Could you identify that individual for the record, please? Will he be testifying?

Dr. LAWRENCE. I will be referring technical questions to him as needed, sir.

Mr. MICA. Maybe he could pull up a chair. Could you again identify him for the record, and his title?

Dr. LAWRENCE. Certainly. Accompanying me is Dr. Gary Ellis, who is the Director of the Office for Protection from Research Risks, National Institutes of Health.

Mr. MICA. Thank you.

We also have Dr. Mark Yessian, Regional Inspector General for Evaluations and Inspections, the Office of Inspector General, the U.S. Department of Health and Human Services. Dr. Yessian, do you have anyone accompanying you who will be testifying?

Mr. YESSIAN. Yes, I do, Mr. Chairman.

Mr. MICA. Could you identify that individual for the record and his title?

Mr. YESSIAN. With me is Laura McBride, she's a policy analyst in our Boston office and was a major contributor to our work on IRBs.

Mr. MICA. Thank you.

We also have Dr. Eric Cassell, Commissioner of the National Bioethics Advisory Commission. Dr. Cassell, are you by yourself today?

Dr. CASSELL. No, I also have somebody with me.

Mr. MICA. Could you identify that individual and also give us his title?

Dr. CASSELL. Yes, Dr. Eric Maslin, is who is the Executive Director of the National Biology Commission and who is right here.

Mr. MICA. Welcome. Pull up a chair, please.

Finally, is it Dr. John Oldham?

Dr. OLDHAM. Right.

Mr. MICA. Director of the New York State Psychiatric Institute. Do you have someone accompanying you, Doctor?

Dr. OLDHAM. Yes, I do.

Mr. MICA. Could you identify that individual and their title, for the record?

Dr. OLDHAM. With me is Dr. Timothy Walsh who was former chair of the IRB at the New York State Psychiatric Institute.

Mr. MICA. Thank you. I guess this will be our largest panel, Mr. Towns, in history. But we welcome each of you. We appreciate your participation in the hearing today, and helping us to find out how we can do a better job, and again, protecting people who participate in medical research and also making certain that we fulfill our legislative oversight responsibilities.

With that, what we will do is begin, first I'll swear in all the witnesses that are here, and we will limit the principal witnesses to 5 minutes, approximately, of oral presentation. Then we'll proceed to questions after we've heard from all of the witnesses, and get their responses.

However, I might say that upon request of the subcommittee, we will be glad to enter into the record, and it will be a full record of

your statement, such as this house record. Any additional supporting information or documents, upon request, will be made part of the record. So again, I welcome you.

If you will please all stand. Raise your right hands.

[Witnesses sworn.]

Mr. MICA. The witnesses answered in the affirmative.

Thank you and welcome each of you. We will start with Dr. Arthur J. Lawrence, who is the Deputy Assistant Secretary for Health in the Office of Public Health and Science. Welcome, sir, and you are recognized.

STATEMENTS OF ARTHUR J. LAWRENCE, Ph.D., DEPUTY ASSISTANT SECRETARY FOR HEALTH, OFFICE OF PUBLIC HEALTH AND SCIENCE, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY GARY ELLIS, DIRECTOR, OFFICE OF PROTECTION FROM RESEARCH RISKS, NATIONAL INSTITUTES OF HEALTH; MARK YESSIAN, REGIONAL INSPECTOR GENERAL FOR EVALUATIONS AND INSPECTIONS, OFFICE OF INSPECTOR GENERAL, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY LAURA McBRIDE, POLICY ANALYST; ERIC CASSELL, M.D., COMMISSIONER, NATIONAL BIOETHICS ADVISORY COMMISSION, ACCOMPANIED BY ERIC MASLIN, EXECUTIVE DIRECTOR, NATIONAL BIOLOGY COMMISSION; AND JOHN OLDHAM, M.D., DIRECTOR, NEW YORK STATE PSYCHIATRIC INSTITUTE, ACCOMPANIED BY TIMOTHY WALSH, M.D., FORMER DIRECTOR OF THE IRB AT THE NEW YORK INSTITUTE

Dr. LAWRENCE. Thank you, Mr. Mica.

Mr. MICA. You might have to pull that mic up closer.

Dr. LAWRENCE. Thank you very much, Mr. Mica, Mr. Chairman and members of the subcommittee, good morning. As Mr. Mica as pointed out, my name is Art Lawrence, I am Assistant Surgeon General and Deputy Assistant Secretary for Health Operations in the Office of Public Health and Science within the Office of the Secretary of the Department of Health and Human Services. I am accompanied this morning by Dr. Gary Ellis, Director of the Office for Protection from Research Risks which is currently within the National Institutes of Health. Dr. Ellis also chairs the interagency agency committee on protecting research subjects, in which 17 Federal departments and agencies participate.

We are pleased to appear before the subcommittee to describe our well developed, yet ever evolving system of protection for research subjects. I've submitted the Department's written testimony for the record. I ask that I be permitted to briefly summarize a few highlights from that testimony, and that my written testimony be entered into the record in full.

Mr. MICA. Without objection, the entire statement will be made part of the record.

Dr. LAWRENCE. Thank you sir. Together with Dr. Ellis I'll then be happy to entertain any questions the committee members might have concerning the importance of this subject meeting.

First, Dr. Satcher has asked that I extend his best regards and his personal regrets for not being able to be here with you today. He has also asked me to extend his personal gratitude to you, Mr.

Towns, for the leadership that you have taken in promoting high energy efforts to eliminate racial and ethnic disparities in health status in the United States. He looks forward to continuing to work with you on this and other matters of importance to the public's health.

He also asked me to relate to you that he shares your concerns about research that is conducted on populations that lack diversity. And in particular, about research that is conducted entirely in minority populations, unless there is a clear and compelling need to do so. As the letter submitted today to Congressman Towns states, "The Department has recognized the need to increase diversity of participants in clinical trials and has taken many steps to accomplish that in federally funded research." A good example of this is seen in the diversity of the Women's Health Initiative studies. The Department is committed to continue these efforts until our goals are met. In addition, we have made a commitment to involve communities in the design and conduct of research and are moving forward with plans to be sure that research addresses the needs of communities and is responsive, considerate of community concerns.

This year has marked a quarter century of the formal promulgation of the Department's regulations for the protection of human subjects in research. This enduring and vigorous system of protections is designed to prevent physical injury, psychological injury, and harm to the dignity to the research subjects as biomedical and behavioral scientists pursue new knowledge for the common good. We are always interested in improving the system to make research as safe as possible.

My written submission, gentlemen, outlines in some detail the multiple layers of protection for human subjects. These feature at least half dozen levels of protection. They include the system of institutional review boards or IRBs, the keystone of the system. These are boards of scientists and nonscientists who independently review research involving human subjects. By regulation, the Department and 16 other Federal agencies cannot provide funds for human subject research unless an IRB approves the protocols for such studies. Once such research is underway, the IRB must conduct continual review of the research at intervals that are appropriate to the degree of risk, at least once a year.

Exerting oversight over the whole process are OPRR and when investigational drugs, devices or biologics are involved, the Food and Drug Administration as well. An additional layer of review which may be employed especially in large studies is an independent data and safety monitoring board or DSMB. These bodies are appointed to oversee and evaluate the research investigation. DSMB reviews accumulated study data and makes recommendations on continuation or modification of research or clinical studies involving human subjects. It is OPRR's role to make certain that the IRB process works at institutions within its jurisdiction.

OPRR has taken a number of actions to bolster effective oversight of individual IRBs on a variety of fronts. We believe that with this system of IRBs that the risks are minimized by using research consistent with sound research design and which do not unnecessarily expose subjects to risks. It helps insure that the risks are reasonable to anticipated benefits, that the selection of subjects is

equitable, that there are proper informed consents and that the rights and welfare of subjects are maintained in other ways as well. IRBs watch out especially for research involving children, prisoners, pregnant women, and individuals with mental disabilities. They also guard the rights and safety of other vulnerable populations, including the economically disadvantaged, and individuals who are also educationally disadvantaged.

It is the IRB's responsibility to assure that additional safeguards are included in studies involving any of these responsibilities.

OPRR oversees implementations of the regulations in all department facilities as well as domestic or foreign institutions or sites receiving Federal and Health and Human Services funds. OPRR requires all departmental agencies and extramural research institutions that conduct research involving human subjects to set forth the procedures it will use to protect human subjects in a policy statement formally called an assurance of compliance. This is a written commitment to ethical principles, and institutional procedures that are adequate to safeguard the rights and welfare of human subjects. The assurance statement becomes a specific instrument that OPRR uses to gauge an institution's compliance with human subject protections if there is a problem.

This description, of course, gentlemen, is a brief outline of the human subjects research protection system. Additional details involving informed consent regulations and research education training methods are included in my written submission.

I wanted to take a final moment here to convey a few facts about what the Department is doing to strengthen and expand the significant human research subjects protection apparatus. What I've outlined mandates a strong and effective OPRR operation. Responding to other concerns in May of this year, an expert panel transmitted a report to the Director of the National Institutes of Health where OPRR is now located. That report recommended that OPRR be relocated from NIH to the Office of the Secretary. It also suggested that the OPRR Director be at the Senior Executive Service or SES level following that transfer.

Third, it was recommended to the Secretary that an independent advisory committee be created, this is the committee which Mr. Towns has just referred to, to provide guidance and to assist in standard setting and review the operation of the OPRR.

Finally, the report suggested that resources currently available to the OPRR may be inadequate for fulfilling its mission. In turn, the Director of NIH transmitted its report to the Secretary indicating agreement with the panel in recommending that the Secretary accept and act on its findings.

In August the Secretary took action on the central recommendations and findings and asked Dr. Satcher to undertake review processes to determine whether to relocate OPRR as a unit or rather to move only the human subjects protections component. A work group was formed to address organizational structure and management consultant has been engaged to examine the question of resources. In October the Secretary accepted the recommendation that the newly relocated office focus solely on human subjects protection with animal welfare functions remaining at NIH. The man-

agement study has not been completed yet and a target date has been set for completion of activities of March 2000.

Finally, the Department has currently put out for comment a notice of proposed rulemaking or an NPRM on privacy. It shows a commitment to reviewing the human subjects protections regulations with an eye toward enhancing the privacy protections of research subjects. This is yet another example of the Department's commitment to another important area of strengthening protections for human research subjects.

We believe we have a system in place which to the greatest degree possible minimizes the potential for harm, enables and protects individuals' autonomous choice and promotes the pursuit of new knowledge.

Thank you, Mr. Chairman, and members for the opportunity to address you this morning on this critical topic. Dr. Ellis and I will be pleased to answer any questions you may have.

Mr. MICA. Thank you.

[The prepared statement of Dr. Lawrence follows:]

Testimony of
Arthur J. Lawrence, Ph.D.
Assistant Surgeon General &
Deputy Assistant Secretary for Health (Operations),
Office of Public Health and Science,
Department of Health and Human Services

Before the
Subcommittee on Criminal Justice, Drug Policy and Human Resources
Committee on Government Reform
United States House of Representatives

Thursday, December 9, 1999
New York, NY
10:30 a.m.

Mr. Chairman and Members of the Subcommittee:

I am Art Lawrence, Assistant Surgeon General & Deputy Assistant Secretary for Health, Office of Public Health and Science, within the Office of the Secretary of Health and Human Services. I am accompanied by Gary B. Ellis, Director, Office for Protection from Research Risks, within the Office of the Director of the National Institutes of Health. Dr. Ellis also chairs the interagency committee on protecting research subjects, in which17 Federal departments and agencies participate. We are pleased to appear before the Subcommittee to describe our well-developed, yet ever-evolving, system of protection of human research subjects. My testimony today thus describes a responsibility of enormous weight.

First, Dr. Satcher has asked that I extend his best regards and his regrets for not being able to be here with you today. He has also asked me to extend to you his personal gratitude for the leadership that you have taken promoting high energy efforts to eliminate racial and ethnic disparities in health status in the United States. He looks forward to continuing to work with you on this and other matters of importance to the public health.

Dr. Satcher asked me to relate that he shares your concerns about research that is conducted in populations that lack diversity, and in particular, about research that is conducted in entirely in minority populations, unless there is a clear and compelling reason to do so. As you know, the Department has recognized the need to increase diversity of participants in clinical trials, and has taken many steps to accomplish this in federally funded research. A good example of this is seen in the diversity of the Women's Health Initiative studies. The Department is committed to continue these efforts until our goals are met.

In addition, we have made a commitment to involve communities in the design and conduct of research, and are moving forward with plans to be sure that research addresses needs of communities and is responsive to community concerns.

This year marks the 25th anniversary of the formal promulgation on May 30, 1974 of the Department's regulations for Protection of Human Subjects in research (Title 45 Code of Federal Regulations Part 46). This enduring and vigorous system of protections is designed to prevent physical injury, psychological injury, and harm to the dignity of research subjects, as biomedical and behavioral scientists pursue new knowledge for the common good. We are always interested in improving the system to make research as safe as it possibly can be.

This system of protection of human subjects in research is based on a succession, or chain, of judgments made by people in the context of federal regulations. Thoughtful people, often volunteering large amounts of their time, look at research protocols and weigh risks and potential benefits. There is no computer program for this; there is no generic formula. One size doesn't fit all. This is custom work.

Multiple Layers of Protection for Human Research Subjects

Who is involved in protecting human subjects? The architecture of the current system involves at least half a dozen levels of protection. First, and foremost, there is the interaction between the research volunteer and research investigator. This is where the informed consent process takes place. It must be an ongoing, dynamic process, as new information becomes available or is desired. The informed consent document, or form, is one component--the written component--of the informed consent process. I will describe the particulars of informed consent in a moment. There may also be other parties involved, such as nursing, scientific, or medical staff other than the principal investigator. There may be a consent auditor or monitor, or an advocate for the research subject.

The Institutional Review Board is, by federal regulation, to be established at the local level and has a minimum of five people, including at least one scientist, one nonscientist, and one person not otherwise affiliated with that institution. The nonscientist must be present to achieve a quorum. The local IRB at the research site is the keystone of our system of protection of human subjects. No human-subjects research may be initiated, and no ongoing research may continue, in the absence of an IRB approval. By regulation, DHHS and 16 other federal departments and agencies cannot provide funds for human subjects research unless an IRB approves the protocols for such studies.

IRB review is 1) prospective and 2) continuing review of proposed research by a group of individuals with no formal involvement in the research. Ideally, it is a local review, by individuals who are in the best position to know the resources of the institution, the capabilities and reputations of the investigators and staff, and the prevailing values and ethics of the community and likely subject population.

Once research is underway, the IRB must conduct continuing review of the research, at intervals appropriate to the degree of risk--in any event, at least once per year. I will return to the responsibilities of the IRB in a moment.

In most circumstances, there are additional officials outside of the formal IRB structure who also play a role in reviewing components of research. For example, the executive officials of the research site (e.g., dean, department chair, and research administrators). Each has the authority to express specific concerns about human-subjects issues. Exerting oversight of the whole process are OPRR and, when investigational drugs, devices, or biologics are involved, the Food and Drug Administration (FDA).

An additional layer of review that may be employed, especially in large studies, is an independent Data and Safety Monitoring Board (DSMB), appointed to oversee and to evaluate the research investigation. DSMBs are usually appointed by, and report to, the funding organization--not the investigators or the institution doing the study. At periodic intervals during the course of the study, the DSMB reviews the accumulated data and makes recommendations on the continuation or modification of the study. A study can be stopped prematurely because of a toxic effect, or because a strong positive effect was seen and it would be unethical to continue with some subjects not receiving the intervention which has demonstrated benefit. While the most of the studies halted for these reasons are as the result of decisions of the investigator or sponsor, the DSMB plays a significant role in large randomized blinded trials.

It is OPRR's role to make sure that the IRB process works at institutions within OPRR's jurisdiction. To give you a sense of the kinds of problems that do occur and actions taken to address them, I will relate brief accounts of some actions taken by OPRR. In one well-publicized instance, the concern was the proper explanation of risks in the informed consent process for a study involving schizophrenia. OPRR 1) rebuked the Institutional Review Board for poor oversight of the informed consent process, 2) directed that the informed consent process be revised, and 3) instituted close monitoring of the institution's human-subjects activities. In a second instance, the concern was misuse of an expedited IRB review process. OPRR identified a failure of leadership within the Institutional Review Board, and the IRB Chairman subsequently resigned. At a third institution, the concern was whether or not the IRB was properly conducting the required continuing, annual review of research. The institution demonstrated to OPRR that some 2,000 research protocols involving human subjects had, indeed, received continuing review in accord with DHHS regulations.

Institutional Review Boards

Let me turn briefly to the specific responsibilities of the Institutional Review Board. In the main, IRB review assures that:

- risks are minimized by using procedures that are consistent with sound research design and which do not unnecessarily expose subjects to risk and, whenever appropriate, by

using procedures already being performed on the research subjects for diagnostic or treatment purposes;

- risks are reasonable in relation to anticipated benefits;
- selection of subjects is equitable;
- there is proper informed consent; and
- the rights and welfare of subjects are maintained in other ways as well. This is particularly important when subjects are likely to be vulnerable to coercion or undue influence.

What populations are judged to be vulnerable? IRBs watch out especially for research involving children, prisoners, pregnant women, individuals with mental disabilities, individuals who are economically disadvantaged, and individuals who are educationally disadvantaged.

Federal regulations provide extra protection for vulnerable subjects in several ways. If an IRB regularly reviews research that involves a category of vulnerable subjects, consideration must be given to including as IRB members one or more individuals who are knowledgeable about, and experienced in working with, the vulnerable subjects. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, IRBs must see that additional safeguards are included in the study protocol. Specific, detailed requirements are written into DHHS regulations pertaining to pregnant women, fetuses, human ova fertilized in vitro, prisoners, and children involved in research.

Once research is initiated, IRBs have continuing responsibilities. These include:

- The conduct of continuing review at intervals appropriate to the degree of risk, and in any event, not less than once per year.

- Authority to observe or have a third party observe the consent process and the research.

- Receipt of prompt reports from investigators of any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with the IRB's requirements or determination, or with the regulations.

- Authority to suspend or terminate IRB approval of research that is not being conducted in accord with the IRB's requirements or that has been associated with unexpected serious harm to subjects.

- IRBs are also responsible for monitoring for the emergence of adverse effects, such as unacceptable and risky responses of human subjects within the research protocol and taking prompt appropriate action .

Assurance of Compliance with Human Subjects Regulations

The DHHS regulations for Protection of Human Subjects are not a set of rules that can be applied rigidly to make determinations of whether a proposed research activity is ethically "right" or "wrong." Rather, this is a framework in which investigators, IRB members, and others can ensure that adequate efforts have been made to protect the rights and welfare of research subjects.

OPRR oversees implementation of the regulations in all DHHS facilities as well as domestic and foreign institutions or sites receiving DHHS funds. OPRR requires that each DHHS agency and extramural research institution that conducts research involving human subjects sets forth the procedures it will use to protect human subjects in a policy statement called an "Assurance" of compliance. At OPRR's discretion, institutions with a large volume of research and demonstrated expertise in human subjects protection may be granted a Multiple Project Assurance. A Multiple Project Assurance, as the term implies, is an institution's pledge of full human subject protections for multiple projects at the institution. By federal regulation, OPRR has authority for approving an Assurance at DHHS-funded institutions for federal-wide use.

An Assurance statement is a formal, written commitment to: 1) widely held ethical principles; 2) the DHHS regulations for Protection of Human Subjects; and 3) institutional procedures adequate to safeguard the rights and welfare of human subjects. The terms of the institution's Assurance are negotiated with OPRR. The detailed, written Assurance statement becomes the instrument that OPRR uses to gauge an institution's compliance with human subject protections if there is a problem.

The DHHS assurance process is due for streamlining, so that OPRR can devote more resources and effort to working with institutions to better educate IRB members, IRB staff, and research staff. In recent months, OPRR has been retooling its intensive Assurance effort to redirect it toward education. As the human subjects protections activities are transferred to a new organizational structure, education and prevention activities will be intensified. Please know that OPRR will not abandon its current preemptive oversight procedures (i.e., negotiation of institutional assurances to comply) before putting in place an education program for assuring competency-based compliance.

Informed Consent

All present today know how integral--how crucial--the process of informed consent is. Many have a general picture of informed consent, and it is useful to add higher resolution to that picture. DHHS regulations specify 14 elements of informed consent, 8 of which are required:

1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

2) A description of any reasonably foreseeable risks or discomforts to the subject.

3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

A researcher who seeks to recruit an individual for research without conveying these elements of information in language understandable to the potential subject is not obtaining *informed* consent.

Research, Education, and Training

The specificity of Federal regulatory language on informed consent, its endurance through many years, and the enthusiasm with which we all adhere to it all belie the fact that little empirical work exists to document the degree of understanding achieved by research participants. There is a scarcity of data that bear upon, for example: 1) research subjects' comprehension of a study's methods and procedures; 2) subjects' understanding of relative risks and benefits of participation; 3) subjects' understanding of confidentiality and any exceptions to confidentiality; and 4) subjects' understanding of the implications of withdrawal from a study. Such data are needed to aid in designing informed consent procedures that are readily comprehended by prospective participants and, at the same time, impart all critical information.

NIH has recently taken major steps to bring improved understanding to informed consent, including the award in 1997 of fourteen, 3-year research grants to scientists who are studying informed consent. And, to further education and training, NIH has issued two solicitations for

training initiatives in bioethics. One provides postdoctoral training for individuals who seek a concentrated training experience. The other supports short-term institutional awards to make increased training in bioethics available to a larger number of scientists.

In the World Wide Web era, OPRR has increasingly made information that is useful to IRBs available on our website. We are also committed to vigorous personal consultation with IRBs and institutional officials. (OPRR logs 175 to 200 phone calls per day!) This level of consultation is instrumental in the development of meaningful performance measures for IRBs. OPRR and FDA are scheduled to meet with numerous IRB members and staff in regional conferences in Houston, Tampa, and Portland OR in the next 12 months--the continuation of an ongoing educational conference program that spans two decades. OPRR participated this week in Boston in the largest meeting ever held of human subject protection advocates–some 1,200 attendees at the annual meeting of Public Responsibility in Medicine & Research.

Commitment to strengthen and refresh the Department's effort

Significant advances have been made in the prevention and treatment of disease in recent decades. Advances are, in large part, attributable to research that involves human subjects. At the same time, research methods have been improving and changing in an environment where concerns about human subjects protections have increased as we learn more about the risks and dangers of high tech research.

As the Department's focal point for human subjects protections, the effective and efficient functioning of OPRR in the contemporary environment is extremely important. In fulfilling its responsibilities, OPRR must not only maintain a high level of performance, but also must be perceived as being in a position to exercise maximal influence over assuring that human subjects protections requirements within its authorized domain are afforded to all human research participants.

Responding to concerns, the Director of the NIH convened an expert review panel to address two main areas of OPRR's operations. First, to assess if the NIH-based organizational locus of OPRR remained the most logical and appropriate for its mission; and, second to advise on any need for additional delegated authority to facilitate OPRR accomplishing its mission. The Panel consisted of well respected bioethicists, attorneys, and scientists.

On May 27, 1999, an expert OPRR Review Panel transmitted their report to the Director of NIH. The Panel made the following primary findings:

- OPRR should be relocated from within NIH to the Office of the Secretary;
- The relocated OPRR Director's position should be at the Senior Executive Service level;

- The Secretary should create an independent advisory committee to "provide guidance, assist in setting standards, and review the operation of the office."

- That the ".. Authority presently delegated to OPRR is adequate for it to address the tasks currently assigned to it, but resources available to OPRR may be inadequate for fulfilling its mission."

In turn, the Director, NIH transmitted the Panel's report to the Secretary indicating their agreement with the Panel and recommending that the Secretary accept and take action on their findings.

In August 1999, the Secretary took action on the central recommendations and findings of the Panel. In addition, she asked the Assistant Secretary for Health and Surgeon General (ASH/SG) to undertake two distinct review processes. She asked that the ASH/SG review the OPRR organization to determine if it would be preferable to relocate OPRR as an intact unit, or to relocate only the human subjects protections component and further requested that a thorough review of resources be conducted. A work group was formed to address the question of organizational structure for the relocated office and a management consulting firm was engaged to examine the question of resources.

In October 1999, the Secretary accepted the recommendation that the newly relocated office focus solely on human subjects protections with animal welfare functions remaining at the NIH. The steps necessary to relocate the human subjects protections components and form a new organizational structure are proceeding. The management study addressing resource questions has not yet been completed. A target of March 2000 has been set for the completion of relocation activities.

The Department currently has out for comment a Notice of Proposed Rule Making (NPRM) on health privacy that contains our commitment to reviewing the human subjects protections regulations with an eye toward enhancing the privacy protections of research subjects. The NPRM solicits comments on how the privacy protections or research subjects can be enhanced and cites that the Secretary of HHS will also consult with other affected departments and agencies. This is another example of the Department's commitment to another important area in strengthening protections for human research subjects.

Conclusion

Our collective goal is to continuously strengthen our system of human-subjects protection from the federal side and from the institutional side as well. Many promising approaches that IRBs might take are, demonstrably, already within their authority to take. In the final analysis, Mr. Chairman and Members of the Subcommittee, research investigators, institutions, and we are stewards of a trust agreement with the people who volunteer to be research subjects. We have a system in place that to the greatest degree possible 1) minimizes

the potential for harm, 2) enables and protects individual, autonomous choice, and 3) promotes the pursuit of new knowledge. By doing so, we protect the rights and welfare of our fellow citizens who make a remarkable contribution to the common good by electing to volunteer for research studies. We owe them nothing less than our best effort.

Thank you, Mr. Chairman. We are pleased to answer any questions about our system for safeguarding the rights and welfare of human research subjects.

Mr. MICA. We'll hear now from our second witness, Mark Yessian. Dr. Mark Yessian is Regional Inspector General for Evaluations and Inspections for the U.S. Department of Health and Human Services. Welcome. The chair will recognize him.

Mr. YESSIAN. Mr. Chairman, Congressman Towns, the current system of protecting human subjects who participate in medical research is in need of major reform. This is a conclusion we emphasized in a June 1998 report; it's one that we reiterate here today.

Our June 1998 report was based on a year-long inquiry into the work of the institutional review boards. That inquiry led us to sound a warning signal that the effectiveness of the boards is in jeopardy.

Here's what we based that on: IRBs review too much, too quickly with too little expertise. They conduct minimal continuing review of approved research. They face conflicts that threaten their independence. They provide little training for investigators and board members. And, not least of all, they must cope with major changes that are fundamentally transforming the research environment from what it was a quarter of a century ago when the current Federal protections were put in place. In our report we made numerous recommendations to the National Institutes of Health and to the Food and Drug Administration. At the core of them was a search for ways to give IRBs more flexibility so they could do their job better, but to hold them much more clearly accountable for results.

Let me provide an update, if I could, on what's happened in the year and a half or so since we issued our report. First, I'd say there are some encouraging developments. At the Federal level, the most notable action has been an increased enforcement effort by the Office of Protection from Research Risks [OPRR]. In the year prior to our report, OPRR had made only one site visit to investigate the adequacy of an IRB's efforts. Since that time, it has made numerous site visits, some very high profile and some resulting in the actual suspension of federally funded research at major medical centers.

At the local level, a number of institutions have put more resources into their IRBs and a number of IRBs have undertaken training and other educational kinds of initiatives intended to sensitize principal investigators and IRB board members to issues involving human subject protection. Then also at the professional level it's important to note there's some stirring there, too. There's a movement toward certifying IRB administrators and one toward private accreditation of IRBs. Both of these movements have some significance.

But as important as these developments are, the system of protections provided by IRBs remains in jeopardy. From the ground up, if you look at IRBs, you see the same danger signs. Expanded work loads, quick reviews, threats to their independence, inadequate information, insufficient training, minimal outside representation. Moreover, and this is the basic point, the underlying pressures on IRBs continue to build and to make it difficult for them to do their job adequately.

Let me touch on three of those pressures. The most important one is the increased commercialization of the research environ-

ment. Industry sponsors, anxious to bring new products to market and to contain their development costs, seek to expedite the clinical trials process and to conduct their trials in the quickest, most efficient settings. For IRBs, this means doing more quicker and better. It also means that it can be quite difficult to slow down the research process by raising nettlesome questions for instance, about the adequacy of the informed consent process.

A second pressure is the continuing and escalating pressure on the IRB members themselves. Most of the time these are volunteers that serve on these boards. They find it difficult to spend the time it takes to review proposals that are increasing both in numbers and complexity.

Finally, I'll note there's an intensified quest for human subjects. If you look at this as a supply-demand situation, we have a substantial unmet demand for human subjects. This heightens recruitment pressures for research sponsors and investigators and leaves IRBs with many difficult questions to face. For instance, should they be concerned about recruitment bonuses that sponsors give to investigators for subjects? Should they be concerned about the mining of patient data bases to find potential human subjects? What about the payment of fees to physicians referring their patients as potential subjects? What are the standards or guidelines to answer such questions? Where are they?

We end up as we did in 1998 calling for a much stronger Federal presence here, and I'll just touch four of the issues that we highlight. There are others, but certainly one would be more extensive onsite performance based reviews of IRBs. The OPRR has started this. It's a good start, but only a start. We recommend this kind of effort intensify and that it conduct both unannounced and announced site visits.

We should also not forget the Food and Drug Administration here. They are actually onsite more often than the OPRR, and have a substantial responsibility here. As we said before, we think it's essential that they broaden their reviews to go beyond simple compliance matters and focus more on performance.

My second point is that we need a strengthened commitment to educational outreach and mandates. Everybody says the answer is always more education, but I think it's really crucial to go beyond the talk and have some action. Action at the Federal level where we provide more in the way of web based tutorials and the like. But also mandates that investigators and board members participate in educational programs concerning human subject protections.

The third direction we're emphasizing is much more extensive representation of non-scientific and non-institutional members on IRBs community members, if you will. It just simply doesn't seem adequate to have situations, as you often do, where there may be 14 or 15 IRB members and one, maybe two from outside the institution. This noninstitutional member can provide a vital counterbalance to the kind of pressures IRBs face. It's a way of sharpening the focus on subjects and what is in their best interest.

And last, as Congressman Towns has already referred to, we simply need a mandate to register IRBs with the Federal Government. This need not be a major burden on anybody, but how can

we provide effective oversight and guidance if we don't even know who the IRBs are and where they're at. So some kind of registration requirement with minimally descriptive information would seem to be important.

In closing, I'd like to emphasize that notwithstanding what may sound like a rather harsh critique, we recognize the major contributions that investigators, sponsors, IRB members and staff are making in this area. There are a lot of committed, dedicated people here, but they work in a system that needs to be reformed. That's the basic point. Such reform is essential to provide necessary protections for human subjects. It's also essential to sustain the progress we are making in clinical research.

Thanks for the opportunity to testify, we are certainly open to questions.

Mr. MICA. Thank you.

[The prepared statement of Mr. Yessian follows:]

Testimony
Before the Committee on Government Reform
Subcommittee on Criminal Justice, Drug Policy and Human Resources
United States House of Representatives

Institutional Review Boards:
A System of Protections Still in Need of Reform

Statement of
Mark R. Yessian, Ph.D.
Regional Inspector General for Evaluation and Inspections

December 9, 1999

Office of Inspector General
Department of Health and Human Services

For Release on Delivery
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Thursday December 9, 1999

Good morning. I am Dr. Mark R. Yessian, Regional Inspector General for Evaluation and Inspections, in the Office of Inspector General's Boston office, U.S. Department of Health and Human Services (HHS). I am pleased to testify at today's hearing on the Federal role in protecting human subjects of medical research. My testimony will focus on Institutional Review Boards (IRBs), the bodies that for more than 20 years have been charged under Federal law with ensuring human-subject protections. With me is Laura C. McBride who was a key architect of these studies.

Mr. Chairman, the current system of protecting human subjects in medical research is in need of major reform. This is a conclusion we emphasized in a series of reports in June 1998. It is one we reiterate today.

BACKGROUND

In the late 1970s, Federal regulations were established requiring institutional review boards to review research protocols. The review is required to ensure human subjects are protected and are adequately informed of the risks and benefits of participating in research. Within the Department of Health and Human Services (HHS), both the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) have responsibilities for human-subject protections and oversight of IRBs. NIH's Office for Protection from Research Risks, however, will soon be relocated to the Office of the Secretary for HHS

where responsibility will transfer to the Assistant Secretary for Health. (For further background on IRBs and their functions, see the primer at the end.)

Background on Our Inquiry

In mid-1997, we initiated a broad, systemic review in response to concerns raised in a prior Office of Inspector General study. In that study, we examined clinical trials involving four investigational medical devices, and, in each case, discovered limitations related to IRB review. These concerned serious matters such as the implantation of a device in three times the number of human subjects specified in the IRB-approved research protocol, the initiation of a research effort without the changes called for in the informed consent document, and the continuation of a research project for six weeks beyond when the IRB had suspended it.

We were also aware of concerns about the IRB system raised by others—for instance, the Advisory Committee on Human Radiation Experiments and the General Accounting Office. Both groups raised questions in their respective reports about the adequacy of the IRB review process.

In our most recent inquiry, we conducted a broad-based analysis of the IRB system in order to gain an in-depth understanding of (1) the challenges facing IRBs and (2) how the IRBs and the Federal government were meeting these challenges. Toward that end, we developed

a multi-faceted methodology drawing on many sources. These included analyses of Federal records; an extensive literature review; site visits to IRBs in 6 academic health centers; additional site visits accompanying FDA inspectors; a survey on the electronic e-mail forum for those associated with IRBs; and the systematic gathering of data from representatives of about 75 IRBs. This inquiry resulted in four reports issued in June 1998.

FINDINGS

Our overriding finding in these reports was that the system of protections, which has been so carefully developed over the years, is in need of reform. We based this conclusion on six main findings. We reiterate them below.

1. IRBs Face Major Changes in the Research Environment.

The research environment has undergone significant change in the 20 years since the Federal IRB regulations were first established. In the late 1970s, research was most often conducted by a single investigator at an academic medical center under government funding. Today, almost the opposite is true. Many research protocols are now multi-center trials involving thousands of subjects, numerous investigators and institutions spread out across the country or even the world. Each institution has little knowledge of what is occurring at other sites, if problems have arisen, or even if other IRBs have called for changes in the protocol. A greater proportion of research is funded by commercial sponsors. Research is conducted

increasingly at sites outside of academia where institutions can more easily accommodate commercial sponsors desire for quick turnaround and efficient research conduct. IRBs feel pressure to accommodate these sponsors for whom time is money.

2. IRBs Review Too Much, Too Quickly, with Too Little Expertise.

IRBs, composed mainly of volunteer members, are working under increasing strains. More and more research is being conducted and, as a result, IRBs across the country are inundated with protocols to review. Some of the sites we visited are now reviewing more than 2,000 protocols annually. These IRBs are also being flooded with adverse-event reports from the multi-center trials they oversee. In an effort to cope with the increased workload, many IRBs are forced to rely on a pre-assigned reviewer to examine and summarize research plans. In some IRBs, unless one of the assigned reviewers raises a question or concern about the research, the board engages in little or no discussion at its meeting. Some IRBs have been able to increase the length of their meetings, but many others are forced to squeeze more reviews into a fixed block of time.

Science is becoming increasingly complex and many IRBs find that they lack sufficient scientific expertise on their boards or staffs to adequately assess protocols. This is particularly evident for protocols involving advanced biomedical techniques—such as genetic testing—that raise scientific issues as well as moral and ethical questions that may not be apparent to the untrained eye.

3. IRBs Conduct Minimal Continuing Review of Approved Research.

The IRBs' ongoing review of research can serve as an important safety net for human subjects. The review involves a re-review of the protocol and an analysis of the adverse event data to ensure the risk to subjects is minimal. However, continuing review has become a low priority and is also often limited to a paper-based review at many IRBs. Board members and officials we spoke with reported that they seldom left the board room to visit the research site. Although many IRBs would like to, few oversee the consent process.

4. Neither IRBs nor HHS Devote Much Emphasis to Evaluating IRB Effectiveness.

IRBs have little basis for knowing how well they are accomplishing their mission of protecting human subjects. Seldom do IRBs seek out feedback from human subjects or their families. Federal oversight does not compensate for these deficiencies as it, too, is not geared to evaluating effectiveness. OPRR's oversight is limited almost entirely to an up-front assurance process. The assurance is a document stating an institution's commitment to adhere to Federal requirements. Most IRB staff we spoke with told us the assurance has little impact on IRB functioning. The OPRR generally goes on-site only in instances of alleged breakdowns in IRB protections.

FDA oversight involves a more frequent on-site presence. However, their visits focus almost entirely on IRB compliance with the procedural requirements set forth in Federal regulations—such as attendance at review meetings, completeness of minutes, and a review

of the informed consent document. Such matters can be important indicators of performance, but they give FDA little direct feedback on the actual effectiveness of IRBs.

5. IRBs Face Conflicts that Threaten Their Independence.

Research monies, particularly from commercial sponsors, is an important source of revenue and/or prestige for most institutions. For example, at one of the academic medical sites we visited, about 25 percent of the operating budget (nearly $200 million) derives from research activities. This revenue source is increasingly important as medical institutions are squeezed by managed-care cost pressures. An important counterbalance to these sorts of pressures is the perspectives of certain IRB members whose concerns are primarily in nonscientific areas or who are not otherwise affiliated with the institution. However, Federal regulations require only one of each. We found few such "outside" members on the boards.

6. IRBs and Their Institutions Provide Little Training for Investigators and Board Members.

The review process can involve complicated ethical issues and scientific questions. Because of this, the education of board members is important. An understanding of the issues is also essential for research investigators who, themselves, initiate the informed consent process and interact directly with research subjects. However, IRBs face significant obstacles which include not only insufficient resources, but the reluctance of many investigators to

participate in training sessions. For new IRB members, their orientation to the role is seldom much more than a stack of materials to read and on-the-job learning.

RECOMMENDATIONS

We found the stresses on the IRB system to be significant enough for us to make a number of strong recommendations to NIH/OPRR and FDA. The thrust of our recommendations was for a more streamlined approach to providing human-subject protections, both at the local and Federal levels. At the same time, we called for a greater emphasis on accountability, performance, and results. Our recommendations included a number of actions, many of which, in the near-term, could help to address the vulnerabilities in the system. Some of our key recommendations were as follows.

- **Grant IRBs Greater Flexibility but Hold them More Accountable for Results**

We called for eliminating or loosening a number of the procedural requirements that Federal regulations currently impose on IRBs, to allow IRBs to meet the significant challenges facing them. Greater flexibility could allow IRBs, for example, to concentrate their limited time and resources on protocols involving substantial risks to subjects. A *quid pro quo* for allowing IRBs greater flexibility is an increased emphasis on accountability. Therefore, we recommended regular, Federal performance-focused evaluations, whose results should be

made public, and more extensive representation on IRBs of nonscientific and noninstitutional members.

- **Reengineer the Federal Oversight Process**

We suggested reorienting the Federal oversight system to focus on IRB performance. In particular, NIH/OPRR should rework its assurance process so that it rests essentially on an institutional attestation to conform to the Federal IRB requirements in order to free scarce OPRR resources for on-site reviews and education sessions. FDA should search for ways of revamping its inspections, so that they focus less on narrow compliance matters and more on performance issues. FDA and OPRR should combine efforts to require a registration process whereby IRBs would submit basic descriptive information annually to HHS. This simple information would allow Federal bodies to more effectively target their oversight and facilitate dissemination of education materials.

- **Strengthen Continuing Protections for Research Subjects**

The IRB system has long relied on an ethic of trust in the research community. However, trust alone does not provide sufficient continuing protection. IRBs need to be more aware of what is actually happening at the research site. For example, they spend a significant amount of time reviewing and editing the language of an informed consent document—documents that can run up to 20 pages in length. But, they know little about what actually happens in the interaction between subject and investigator.

Another key mechanism of ensuring IRBs' meaningful reviews of approved research is requiring certain outside sources to provide IRBs with valuable information. Data Safety Monitoring Boards oversee many large-scale trials and continually monitor the safety and efficacy of trials. Assessments of adverse events across many disparate sites could help IRBs in their continuing reviews and reduce their workload. Also, the FDA should provide IRBs with feedback on actions it takes against investigators that are engaged in research at the IRBs' institution.

- **Enhance Education for Research Investigators and IRB Board Members**

Investigators are the ones who actually interact with and consent subjects. Investigator education can help convey to investigators that along with the considerable independence that they have in the research process, there exists a significant responsibility to ensure human-subject protections. Investigators, who are adequately sensitized to human-subject protections, can also serve to minimize the need for regulatory intervention by the Federal government or by IRBs themselves. Board members must also be trained on Federal requirements. There are also many hidden ethical issues, particularly with the newer types of research such as genetics, to which IRBs must be sensitive.

AN UPDATE

Our reports were released a year and a half ago. Since then there have been some encouraging developments. But, the system of protections is still in jeopardy and the need for strong federal action is still compelling. I'll close by elaborating on each of these points.

Encouraging Developments

Federal Initiatives. Progress has been made at the Federal level, mainly in the activities of OPRR. In the year before our report was issued, OPRR made only one on-site visit to a research institution. Since that time, it has conducted a number of such visits, including one that resulted in the temporary termination of all federally sponsored research at the Duke University Medical Center. Some of their reviews represent the most probing and results-focused inquires we have found of IRB performance, resulting in strong recommendations to the IRBs. They are also taking a more active role in issuing further educational outreach programs. NIH has issued guidance on the transmittal of information to IRBs from data-safety boards used for trials it funds.

Local Efforts. These Federal efforts, in particular the recent shutdown at Duke University, in tandem with our reports and recent media attention have served as a catalyst for change at

IRBs and their institutions. Many IRB representatives told us that they have been able to garner more support and resources from their institutions. For example, an IRB Chair from a small community research institution called to ask for 20 copies of our report in order to hold their first-ever IRB training program.

Professional Responses. There is a newly developed momentum to certify IRB administrators and to develop a system for the private accreditation of IRBs. Both of these efforts represent potentially important ways of raising the bar in current IRB practice.

A System Still in Need of Reform

As encouraging as the above developments are, the system of protections provided by IRBs remains in jeopardy. The same danger signs are widespread: expanded workloads, quick reviews, threats to IRB independence, inadequate information, and insufficient training.

Underlying pressures on IRBs continue to build and make it more difficult for them to do their job:

- **Increasing Commercialization of Research.** One of the most significant challenges IRBs face is the commercialization of research. Industry is now the largest sponsor of clinical research in the country. With the increasing prominence of industry comes the pressure for "more, faster, better" IRB reviews. Investigators are

expected to recruit subjects quickly and IRBs are prodded for timely approvals of research protocols. IRBs' own institutions are often focused on bringing in important research dollars from industry sponsors. Many see thorough IRB review as a hurdle for their research efforts. Hand in hand with the commercialization of research is the potential for conflicts of interests. It is important to note that these conflicts are prominent in all research settings— academia, industry, and independent— and from all sources of funding.

- **Increasing Burden on IRB Members.** IRB members, who are often volunteers, are increasingly hard-pressed to devote the substantial time required for IRB reviews. They are asked to review more projects, more adverse event reports, many of which occur off site, and analyze complex ethical issues raised by new areas of research (i.e., gene therapies and genetic testing). All of this must be accomplished in a limited amount of time and while members must balance competing responsibilities within their own institution.

- **Increasing Need for Subjects.** Because of the growing amount of research, investigators and research sponsors must find more and more human subjects. The intensified quest for subjects heightens recruitment pressures and leaves IRBs with many difficult questions to confront. Should they be concerned about recruitment bonuses that sponsors give to investigators? What about when investigators mine

patient databases to find potential subjects? Should investigators offer fees to physicians when the physicians refer their patients as subjects? Few guidelines exist to help answer such questions.

Continued Need for Federal Action

A number of IRBs have enacted policies to help balance the pressures and minimize conflicts of interest. However, most IRBs are hard-pressed to keep up with the changing environment around them. Even if they are able to enact changes, they may be at a competitive disadvantage to do so. Research sponsors often view a burdensome and lengthy review process as a negative when deciding which sites will conduct their research. Therefore, we need stronger Federal action. Federal requirements can help safeguard adequate protections and establish a level-playing field among research sites. Adequate protections would also help maintain the integrity of the research enterprise. Just one unfortunate incident can damage public confidence in research and, in turn, limit progress.

We continue to support all of the recommendations offered in our report. We regard the following as particularly significant actions that Federal bodies could take to shore up protections for human subjects.

1. Maintain adequate Federal on-site presence. Visit by Federal bodies can help reinforce to institutions the importance of IRBs. These visits, particularly when conducted randomly, can serve to identify cracks in the local IRB system before problems occur and serve as technical assistance. When unfortunate incidents or complaints do arise, quick Federal responses can provide an outside perspective on necessary corrective actions.

2. Require investigator and IRB member education. The NIH should require that institutions which receive funds for human-subject research under the Public Health Service Act have a program to educate their investigators about human-subject protections. Investigators, before participating in this research, should be asked to sign a written attestation, similar to the one required for FDA research, acknowledging their responsibility for human-subject protections. Also, IRBs should be required to provide an orientation program for new members and a continuing education program for all members before reviewing research funded by NIH or under FDA purview.

3. Require more extensive representation of nonscientific and noninstitutional members on IRBs. The current requirement of only one nonscientific and one noninstitutional member on an IRB is inadequate. This regulation can be met with the selection of just one person; boards often have 15-20 members. "Independent" members can provide an important counterbalance to institutional interests and potential conflicts. They also provide

an important voice which may be attuned to the needs and sensitivities of the community. There should be enough of these members to ensure their voices are heard.

4. Require IRBs register with the Federal government. Current estimates suggest the number of IRBs in the country is somewhere between 3,000 and 5,000. However, no one knows for certain how many IRBs there are, nor where they are. IRBs should be required to register with the Federal government and provide minimal descriptive information annually. Identifying information would help target more effective oversight. Also, it would ensure that Federal bodies be able to more efficiently disseminate important guidance and notices of upcoming educational opportunities.

CONCLUSION

In closing, Mr. Chairman, I would like to underscore that the current system of protections is supported by many conscientious researchers committed to protecting human subjects and many competent, dedicated IRB staff. But the system they function in has become brittle, with a few cracks. The effectiveness of the system is in jeopardy.

It is vital to reform this system so that human subjects receive adequate protections, so that we can confidently recruit the participants we need for clinical research, and so that the research process itself remains on a productive, fast track—one that will improve our understanding of

disease mechanisms and introduce new and effective products and treatments for addressing them. It is particularly important for the Federal government to exert leadership in triggering reform because in an increasingly commercialized, competitive research environment, the Federal government is best suited to establishing the level playing field on which contending parties participate.

Thank you for the opportunity to testify on this most important topic. At this time, I would be happy to answer any questions which you or the other members of the Subcommittee may have.

INSTITUTIONAL REVIEW BOARDS: THE BASICS

What Do They Do?

The responsibilities of IRBs fall into two main categories: initial review and continuing review of research involving human subjects.

Initial Review: IRBs review and approve a research plan before the research is carried out. This review encompasses the research protocol, the informed consent document to be signed by subjects, any advertisements to be used in recruiting subjects, and other relevant documents. In carrying out this review, the boards seek to ensure any risks subjects may incur are warranted in relation to the anticipated benefits, that informed consent documents clearly convey the risks and the true nature of research, advertisements are not misleading, and the selection of subjects is equitable and justified. IRBs focus much attention on the informed consent document as it is the vehicle for providing information to potential research subjects.

Continuing Review: The continuing review process is multifaceted and includes required reviews "at an interval appropriate to the degree of risk but not less than once per year." In addition to this continuing review, study amendments and reports of unexpected adverse experiences by subjects are received periodically and reviewed to ensure that the risk-benefit ratio of the research has not changed and remains acceptable.

Why Were They Established?

As public awareness and concern about the treatment of human subjects in research increased, the need for additional review mechanisms was evident. These concerns grew from stories of the abuse of subjects during the World War II trials at Nuremberg, the promotional distribution of thalidomide resulting in numerous children born with birth defects, the administration of cancer cells to chronically ill and senile patients at a hospital in New York, and others. A 1966 article by Henry Beecher brought prominent attention to human research abuses in medical schools and hospitals citing 22 cases involving highly questionable ethics. The formal requirements for the establishment of IRBs were outlined in regulations stemming from the National Research Act of 1974 and in FDA regulations issued in 1981.

Where Are They Located?

An estimated 3,000-5,000 IRBs can be found across the country. They are most commonly associated with hospitals and academic centers. Boards also exist in managed-care organizations, government agencies (such as the National Institutes of Health, the Centers for Disease Control, and State governments), or as for-profit entities that are independent of the institutions in which the research takes place.

How Are They Organized?

Federal regulations require that boards have at least five members with varying backgrounds. At least one member must have primarily scientific interests, one must have primarily nonscientific interests, and one must be otherwise unaffiliated with the institution in which the IRB resides. A quorum, with at least one member whose interests are primarily nonscientific present, is needed for voting.

How Does the Department of Health and Human Services (HHS) Oversee Them?

Two agencies within HHS share responsibility for IRB oversight: the Office for Protection from Research Risks (OPRR) in NIH and the FDA. The OPRR's main tool for oversight is the assurance document. Any institution that intends to conduct HHS-funded research must have an assurance on file with OPRR. The assurance is a written statement of an institution's requirements and procedures for its IRB and human subject protections. Institutions conducting multiple HHS-supported studies can apply for a multiple project assurance (MPA) which can be renewed every five years. Institutions with smaller HHS-funded workloads, however, use a single project assurance (SPA) for each such project it conducts. The OPRR also conducts a small number of site-visits. The FDA's main mechanism for IRB oversight is the inspection process. The FDA also inspects research sponsors and scientists (known as research investigators).

Mr. MICA. We'll now hear from Dr. Eric Cassell, who is the Commissioner of the National Bioethics Advisory Commission. Welcome, sir. You're recognized.

Dr. CASSELL. Thank you. I would like to thank the chair and members of the subcommittee for the opportunity to appear. I am Eric Cassell, Commissioner of the National Bioethics Advisory Commission. I would appreciate it if the entire statement could be included in the record.

Mr. MICA. Without objection, so ordered.

Dr. CASSELL. I think it would be appropriate if the National Bioethics Commission report and its recommendations be included in the record.

Mr. MICA. Without objection, so ordered.

Dr. CASSELL. Interest in this subject goes back to its very beginnings. It's a society's primary obligation to provide improved ways of protection of subjects in research. But in this instance, there are special problems. During its 18 months of study, NBAC held hearings, heard witnesses from community members to psychiatrists, from OPRR and other experts, and have confirmed the problem of lack of protection or inadequate protection for persons with mental disorders who are subjects of research.

These persons have need for special protection, primarily arising from several things. First of all, persons with mental disorders have a really important need to find adequate treatment, which is often not available outside of the research setting, or at the very least, the most modern treatment is now in the research setting so that they are often forced to go into research protocol to get what they need. They are often stigmatized, and so they don't have the protection of the community that is normally present and often invisible, but is always there, people who know their rights and so forth.

They have varying capacity to consent. Their illness may make it impossible for them to recognize what their needs are, what they should consent to, what they shouldn't consent to at some times, while at other times, they have the same capacity as persons without disorders.

There also are problems that arise from the enthusiasm of investigators, and but most of all I'd like to echo what's just been said, from a lack of education of investigators about ethical issues in research. When you're hot on the trail of something exciting, and when that's your life's work, sometimes enthusiasm overcomes other objectives and people enter into research that otherwise might not, and the subject is a willing participant for the same reasons I noted before. Now, after reviewing all the problems that came before, in fact, we made a number of recommendations. The recommendations which are primarily what this, our large report is about, are 21 in nature. They are currently under review by Federal agencies that are subject to the common rule, and under review by the White House, and we are very hopeful that the role of this committee will in part be to move forward a review of those recommendations, and make them appear in regulations in the future.

There are six categories of recommendations: The first has to do with the nature of IRB's and the importance of having membership

in the IRB of persons from the community, of persons with mental disorders so that they are adequately represented. Also, there are questions that may come before IRBs which are beyond their competence and which should be reviewed by a special panel in the office of HHS that can bring before it problems of a more general nature that should be seen.

Next, the research design for persons with mental disorders have to be more carefully gone over. For one thing, wherever possible, other subjects should be used who do not have mental disorders. There should be great concern about the use of placebo controls in people who have mental disorders because on occasion they may heal again by going back to a placebo state. Certain others, special projects like what happens when somebody has a washout period, that means their medication is removed, they're given time for their illness to appear, which is one thing with diabetes but a different thing with schizophrenia.

Next thing, we were very concerned about the nature of informed consent. It is crucial whether it is clearly known whether a person has the capacity to consent, and in this we requested that there be assessment of individuals with mental disorders by a qualified, independent professional, something that is not used in other areas of research.

Next, there are categories of research relating to levels of risk and the prospective benefit which must be clearly spelled out so people are not subjected to research where there's no benefit possible, but risk is present.

We also recommended that it be possible for there to be certain decisionmakers who are members of the patient's family or are friends and who can represent them when they do not have the capacity to represent themselves.

And finally, we, like everybody else, emphasize the importance of education. But I cannot state too strongly that we have to educate people in IRBs or we have to educate investigators; but then it just sort of trails off. It's not adequate. It requires resources to educate people and requires putting in place those resources and the people to do it, and I'm hoping very strongly that the subcommittee sees the importance of education and sees the importance of adding extra resources.

We used to say that people who had a huge budget but didn't do research, that that was faulty. We should now say that where there's money for research, there should always be money for education of investigators and IRBs about ethical issues in research.

I'd like to conclude by pointing out that NBAC's special mission is to look at the whole system of protection of human subject from research risk. That's our primary obligation, and we are now starting a long and detailed investigation of that issue and we expect to issue a report with detailed recommendations about changes in the IRB system and in the general system to protect human subjects of research. I appreciate very much the opportunity to testify.

Mr. MICA. Thank you.

[NOTE.—The report entitled, "Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity," may be found in subcommittee files.]

[The prepared statement of Dr. Cassell follows:]

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and

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Before the

Subcommittee on Criminal Justice, Drug Policy,

and Human Resources

Committee on Government Reform

U.S. House of Representatives

December 9, 1999

Thank you, Mr. Chairman, and members of the Subcommittee. I am Eric Cassell and I serve as a Commissioner on the National Bioethics Advisory Commission (NBAC). I am also a Clinical Professor of Public Health at Cornell University Medical College. I am pleased to appear before you this morning to describe the recommendations NBAC made in its December 1998 report entitled *Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity*. The report, which was forwarded to the President on January 8, 1999, has been widely circulated. I have made copies available to the subcommittee as part of my written testimony, and note that it is available on the Commission's website (www.bioethics.gov).

Mr. Chairman, there have been several efforts to extend additional regulatory protections for research involving individuals with mental disorders, but these efforts have not been fully successful. In the late 1970s, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission), studied the need for special protections for research subjects with mental disorders in a report entitled *Research Involving Those Institutionalized as Mentally Infirm*. The Department of Health Education and Welfare proposed regulations in 1979, but these were never adopted.

NBAC decided to study this topic as part of its overall mission to advise the National Science and Technology Council (NSTC) and other government entities on appropriate policies, guidelines, and other instruments addressing the bioethical issues arising from research on human biology and behavior. NBAC examined this topic because of the special needs of these persons serving as subjects of research--including the need for more research--but also because of the weaknesses in federal regulations that have persisted for the past two decades. Several highly publicized incidents involving research subjects in this vulnerable population were also brought to NBAC's attention.

During its 18-month study, NBAC heard testimony at 13 separate meetings from members of the public, scientists, former research subjects, their families, and others; obtained nearly 120 public comments during a 45-day comment period on a draft report; reviewed commissioned papers from leading experts in law, medicine, psychiatry, and ethics; and reviewed a small sampling of research protocols in this field.

NBAC found that the nation's scientists have made much important progress on the causes and treatments of mental disorders, and that opportunities to develop new therapies are likely to continue to emerge. The scope of research on mental disorders is expanding significantly and the research environment has become far more complex, involving both a larger societal investment and a greater role for the private sector.

With regard to the protection of human subjects, NBAC concluded that in addition to the existing Federal Policy for the Protection of Human Subjects (also known as the "Common Rule"), "research involving subjects with mental disorders that may affect decisionmaking capacity should be governed by specific further regulations."

As Dr. Harold Shapiro stated in his letter to the President transmitting the report, "While current U.S. regulations note the need to ensure ethical treatment of human research subjects with mental disorders, they provide no specific guidance for IRBs and investigators regarding vulnerable subjects...We believe that this state of affairs is not satisfactory, and that additional federal protections are needed."

NBAC made 21 recommendations that provide both a set of requirements that NBAC believes must be satisfied in all research protocols involving persons with mental disorders, and several additional or optional protections that may be considered, as appropriate, in particular circumstances. Taken together, these recommendations would both enhance existing protections and facilitate broad public support for continued research on mental disorders.

The recommendations fall under six categories: review bodies; research design; informed consent and capacity; categories of research; surrogate decision making; and education, research, and support. Let me summarize some of these.

1. With respect to the recommendations relating to review bodies, NBAC recommends that all Institutional Review Boards (IRBs) that regularly consider proposals involving persons with mental disorders should include at least two members who are familiar with the nature of these disorders and with the concerns of the population being studied (Recommendation 1).

NBAC was persuaded that for research involving greater than minimal risk but that does not hold out the prospect of any medical benefit, subjects could be involved only under the most stringent conditions. In these cases NBAC recommends that the Secretary of Health and Human Services convene a Special Standing Panel to review these protocols at the national level (Recommendation 2). This Standing Panel would include members representing the diverse interests of potential subjects, the research community, and the public. This Panel would provide a national and publicly accountable review mechanism for research. It would be charged with developing guidelines that could be used by local IRBs. NBAC recommends that all federal agencies subject to the Common Rule use this panel, and that a study of its effectiveness be completed within five years.

2. With respect to research design, NBAC recommends that research should not target people with mental disorders when research can be done with other subjects (Recommendation 3). In addition, researchers should describe efforts to minimize risks to subjects, so that IRBs can make an informed risk/benefit assessment, a determination that is especially important when the studies involve placebo controls, symptom provocation, or rapid medication withdrawal (Recommendations 4 and 5).

3. With respect to informed consent and capacity issues, NBAC recommends that no person who has the capacity for consent may be enrolled in a study without his or her informed consent (Recommendation 6). In addition, NBAC recommends that a subject's objection to participation should be heeded even if he or she is confused or is incompetent (Recommendation 7). NBAC also recognized the importance of assessment

of capacity; we recommend that where research involves greater than minimal risk, IRBs should require that an independent, qualified professional assess the potential subject's capacity to consent (Recommendation 8).

4. With regard to categories of research, we made specific recommendations about which criteria IRBs should use when evaluating certain types of research based on the level of risk and the extent to which the study held out the prospect of direct medical benefit to the subjects (Recommendations 10-12).

5. We made five recommendations relating to surrogate decision making. In cases where it has been determined that a research subject lacks or has lost the capacity to make decisions about research participation, NBAC made a series of recommendations specifying who is able to act as a "legally authorized representative" of a research subject and under what situations such a representative may enroll a subject in a study (Recommendations 13-17).

6. NBAC made several recommendations relating to education, research and support (Recommendations 18-21). For example, NBAC recommends that all research sponsors (government, private sector enterprises, and academic institutions) should work together to make the necessary resources available for implementation of the recommendations in its report (Recommendation 21).

Researchers will likely see some of the other recommendations as too restrictive of research and those concerned with the rights of subjects may view them as too permissive. For example, NBAC recommends that in cases where research involves greater than minimal risk, IRBs should often require researchers to obtain an independent assessment of the subject's capacity to consent (Recommendation 8). Some may see this as too great an imposition on researchers and institutions, while some advocates for patients' rights might have hoped to see this recommendation go further, requiring that all research subjects, regardless of the level of risk in a study, be assessed for their capacity. Some will no doubt consider NBAC's recommendations that subjects who are capable of consenting can, under certain conditions, give a "prospective authorization" to their future involvement in research (Recommendation 13), which is an important method for permitting competent persons to express their wishes for participation in studies in the future when they are no longer able to express their wishes. Others may find that this recommendation permits people to be enrolled in research without their express informed consent.

The NBAC report identified those who should be responsible for implementing the recommendations. These include investigators and IRBs, state legislatures, the National Institutes of Health, the Department of Health and Human Services (DHHS), health professionals, federal agencies subject to the Common Rule, and others responsibile for human subjects protections.

NBAC proposed a number of recommendations for regulatory reform, but it did not take a position on whether these reforms would best be accomplished through changes in the

Common Rule, or through the adoption of a new Subpart in the Code of Federal Regulations. More importantly, the Commission made clear its belief that some of these changes could be implemented voluntarily at the local level, emphasizing the following statement in the report: "Regardless of which regulatory route is selected, NBAC encourages researchers and institutions to voluntarily adopt the spirit and substance of these recommendations."

All agencies subject to the Common Rule received a copy of NBAC's report, and were asked by the NSTC for their comments. The report is now under review by both the NSTC and DHHS.

Mr. Chairman, the subject of this hearing comes at an important time in the history of human subjects protections in this country. The opportunity exists to identify and correct deficiencies in the present system, but also to plan for how best to build the system as we move into the next century. In NBAC's view, the enhanced protections recommended in its report will promote broad-based support for further research by engendering greater public trust and confidence that subjects' rights and interests are fully respected.

While this report focused specifically on research involving persons with mental disorders, NBAC's ongoing mandate is to consider the protection of all human subjects in research. We were recently asked by the Assistant to the President for Science and Technology, Dr. Neal Lane, to return to our original charge from the President to examine the current system of human subjects protections. This report has just started, and we would be pleased to keep the Subcommittee apprised of this work as it proceeds.

I would be pleased to discuss any of the report's recommendations in more detail. NBAC (and its staff) would be pleased to work with you as you continue to address these important issues.

Thank you, Mr. Chairman.

Mr. MICA. I can now recognize Dr. John Oldham, director of the New York State Psychiatric Institute. You're recognized, sir.

Dr. OLDHAM. Thank you, Chairman Mica, Congressman Towns. I'd like to thank you for the opportunity to testify today on this important topic. Joining me today is Dr. Timothy Walsh, a research scientist at the New York State Psychiatric Institute and former chair of the Institute's IRB. Also I'd like to request that our entire testimony be entered into the record.

Mr. MICA. Without objection so ordered.

Dr. OLDHAM. It's been approximately 25 years that institutional review boards have been formally carrying out their function and it's appropriate to review the Federal regulations and the IRBs that are at their center. Currently institutions, such as New York Psychiatric Institute, which I'll refer to as NYPI, are required to enter into a multiple project assurance or MPA with OPRR, an agreement which governs research at that facility. Under an MPA, reporting mechanisms that are established for unanticipated problems that involve research risks and for suspension or termination of IRB approval for specific research protocols. OPRR provides oversight of research programs conducted under an MPA and it also conducts investigation of allegations of violations of human subject regulations.

NYPI has chosen to apply the Federal regulations to all of its research, including that which is not federally funded. Elsewhere in the country, however, some non-federally funded research falls outside the scope of Federal regulations. One issue to consider in protection of research participants would be to mandate universal application of the Federal regulations.

The IRB serves an important and useful role in the system of protecting human subject research. NYPI has a highly committed and responsible IRB. As this committee is aware, NYPI was the subject of allegations filed with OPRR regarding a portion of a particular study carried out in 1995. And Dr. Walsh and I testified before the Subcommittee on Human Resources in June 1998.

OPRR conducted a lengthy and thorough investigation to determine whether NYPI complied with the detailed Federal regulations that applied to the research. They were provided with extensive documentation of the study and its IRB review and oversight. They made multiple requests for additional information and received lengthy responses to detailed questions. In March 1999 a team of six OPRR staff and three outside consultants questioned NYPI investigators, IRB chairs and members and institutional representatives at length and reviewed their decisions and actions in light of Federal regulations.

After 16 months of investigation, OPRR concluded that not only were there no deficiencies in the IRB's review of the research and human subject protections provided, it also commended the psychiatric institute's IRB: for its "detailed understanding of the specific requirements of the Federal human subject regulations," and for its members who are, "enthusiastic and dedicated to the protection of human subjects and have the diversity, including consideration of race, gender and cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its ad-

vice and counsel in safeguarding the rights and welfare of human subjects as required under Federal regulations."

The study in question was one component of a larger study which sought to identify factors that contribute to the development of antisocial and violent behavior in young boys, a concern of pressing importance in our country today. It has been scientifically established in adults that violent behavior is correlated with low levels of a brain chemical called serotonin. Serotonin can be indirectly measured by blood tests after the administration of a drug called fenfluramine, a test for serotonin much like a glucose tolerance test, is a test for diabetes, and a cardiac stress test is a test for heart irregularities.

For many years prior to the study at NYPI, fenfluramine studies were a well-established mechanism for measuring serotonin. Researchers outside of NYPI had described experiences with more than 2000 research subjects, including over 200 children and adolescents who had participated in fenfluramine studies. Even after concerns about the long term, large dose safety of the drug led to its withdrawal from approved use for obesity, which did not occur until almost 2 years after the NYPI study was concluded, the FDA still allowed it to be used in small, single dose research studies, since this had always been judged to be entirely safe and indeed, the FDA continues to permit this use today.

The study at NYPI involved the administration of fenfluramine to younger brothers of already adjudicated delinquents. It has been scientifically well-established that these younger brothers are at high risk to develop behavioral problems. In fact, the majority of the boys in the study were described by their teachers and/or family as showing evidence of significant behavioral problems. The process for selecting participants in the overall study was approved by the IRB and did not exclude anyone on the basis of race. The investigators recognized that the study they proposed ultimately needed to be broad-based with a geographically and ethnically diverse sample, but as is generally the case in an initial phase of the investigation, funding and methodological issues dictated beginning with a smaller sample drawn from the surrounding community.

For this reason, investigators obtained information on eligible families from records of the family courts of Manhattan and Bronx. The IRB specifically required that there be no ethnic or racial exclusions as a condition for approving the protocol. The consent process occurred over several visits and children participated only if both parents and children agreed to the procedures at all times. Families were specifically told that participation would not influence any court or correctional decisions. At the time of the selection, all of the older siblings had already been adjudicated.

In the fenfluramine study, a small dose of fenfluramine was given in the form of a single, oral tablet, an amount that has always been judged safe. Although the IRB determined that the study provided no direct benefit to the individual participants, it was anticipated that the children would receive a number of indirect benefits, and they did. The children received expert neuropsychological, general medical and mental health evaluations. Findings from these evaluations led to referrals for visual, dental, pediatric and mental health care, and in the case of children with

educational problems, were used to expedite appropriate educational assistance.

The study helped provide a foundation for a new approach to help parents raise children who are at risk for behavioral problems. Studies to examine the utility of these interventions are now underway with Federal support, including a recent grant from the Department of Education. This is the goal of research, to lead to the development of effective services and treatments.

Again, we appreciate the opportunity to testify at this hearing. We would be happy to respond to your inquiries.

[The prepared statement of Dr. Oldham follows:]

UNITED STATES HOUSE OF REPRESENTATIVES
COMMITTEE ON GOVERNMENT REFORM

SUBCOMMITTEE ON CRIMINAL JUSTICE, DRUG POLICY AND HUMAN RESOURCES
DECEMBER 9, 1999 HEARING

"DO CURRENT FEDERAL REGULATIONS ADEQUATELY PROTECT PEOPLE WHO PARTICIPATE IN MEDICAL RESEARCH?"

Written Testimony of

John M. Oldham, M.D.
Professor of Clinical Psychiatry, College of Physicians & Surgeons, Columbia University
Director, New York Psychiatric Institute

B. Timothy Walsh, M.D.
Professor of Psychiatry, College of Physicians & Surgeons, Columbia University
Co-Chair, New York Psychiatric Institute Institutional Review Board, 1990-1997

Chairman Mica, members of the Government Reform Subcommittee on Criminal Justice, Drug Policy and Human Resources, I would like to thank you for the opportunity to testify today about this important topic. It has been approximately 25 years that Institutional Review Boards (IRB's) have been formally carrying out their functions. This is a time of unprecedented advancement in medical science, and it is also an appropriate time to review the federal regulations and the IRB's that are at their center.

The federal regulations provide rules for institutional review boards (IRBs), which are based on a set of ethical principles outlined in a document known as the Belmont Report[1]. The

[1] The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, produced by The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979).

federal research regulations include detailed regulatory requirements for all research, and mandate specific additional protections for children, prisoners, pregnant women and fetuses.

Currently institutions such as New York Psychiatric Institute that conduct federally funded studies are required to enter into a Multiple Project Assurance (MPA) with the Office for Protection from Research Risks (OPRR), an agreement which governs research at that facility. Under an MPA, reporting mechanisms are established for unanticipated problems involving research risks and for suspension or termination of IRB approval of specific research protocols. OPRR provides oversight of research programs conducted under an MPA. It also conducts investigations of allegations of violations of human subject regulations.

One area of the examination of IRBs and federal research regulation which could be considered is that their coverage is not universal. With the exception of FDA-regulated research, some non-federally funded research may be conducted without the application of federal regulations. While New York Psychiatric Institute, like other major academic institutions, has chosen to apply the federal regulations to all of its research, regardless of whether the studies are federally funded, many studies conducted today fall outside the scope of the federal research regulations.

The IRB serves an important and useful role in the system of protecting human research subjects. New York Psychiatric Institute has a highly committed and responsible IRB. As this committee is aware, the New York Psychiatric Institute was the subject of allegations filed with OPRR regarding a portion of a particular study carried out in 1995 at the Institute, and

Dr. Walsh and I testified before the Subcommittee on Human Resources in June, 1998, about that study. A copy of that testimony is attached to today's testimony.

OPRR conducted a lengthy and thorough investigation to determine whether NYPI complied with the detailed federal regulations that applied to the research. They were provided with extensive documentation of the study and its IRB review and oversight. They made multiple requests for additional information and received lengthy responses to detailed questions. In March 1999, a team of six OPRR staff and three outside consultants questioned NYPI investigators, IRB chairs and members, and institutional representatives at length and reviewed their decisions and actions in light of federal regulations.

After 16 months of investigation, OPRR concluded that not only were there no deficiencies in the IRB's review of the research and the human subjects protections provided, it also commended the Psychiatric Institute's IRB:

- for its "detailed understanding of the specific requirements of the [federal] human subject regulations,"
- for its members who are "enthusiastic and dedicated to the protection of human subjects" and have "the diversity, including consideration of race, gender and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects, as required under [federal] regulations,"

- and for its "established procedures [for ensuring that] additional safeguards have been included in research to protect the rights and welfare of vulnerable subjects."

The study in question was one component of a larger study which sought to identify factors that contribute to the development of antisocial and violent behavior in young boys, a concern of pressing importance in our country today. It has been established in adults that violent behavior is correlated with low levels of a brain chemical called serotonin. Serotonin can be indirectly measured by blood tests after the administration of a drug called fenfluramine, a test for serotonin--much like a glucose tolerance test is a test for diabetes or a cardiac stress test is a test for heart irregularities.

For many years prior to the study at NYPI, fenfluramine studies were a well-established mechanism for measuring serotonin. Researchers outside of NYPI had described experiences with more than 2,000 research subjects, including over 200 children and adolescents, who had participated in fenfluramine studies. At the time of the study in question, fenfluramine was FDA-approved for use in large daily doses for the treatment of obesity over a period of several months. Even after concerns about the drug's safety led to its withdrawal from approved use for such treatment-- something which did not occur until almost two years <u>after</u> the NYPI study was concluded-- the FDA still allowed it to be used in small, single-dose research studies since this had always been judged to be entirely safe, and indeed, the FDA continues to permit this use today.

The study at NYPI involved the administration of fenfluramine to younger brothers of already adjudicated delinquents. It has been scientifically well-established that these younger brothers are at high risk to develop behavioral problems. In fact, the majority of the boys in the study were described by their teachers and/or family as showing evidence of significant behavioral problems.

The process for selecting participants in the overall study was approved by the IRB and did not exclude anyone on the basis of race. The investigators recognized that the study they proposed ultimately needed to be broad-based with a geographically and ethnically diverse sample, but as is generally the case in the initial phase of an investigation, funding and methodological issues dictated beginning with a smaller sample drawn from the surrounding community. For this reason, the investigators obtained information on eligible families from court records of the Family Courts of Manhattan and the Bronx. The IRB specifically required that there be no ethnic or racial exclusions as a condition of approving the protocol. However, the overwhelming majority of individuals reported from the court records and, therefore, the overwhelming majority of participants in these studies were from minority ethnic groups, primarilyAfrican-American and Hispanic. The investigators subsequently submitted to the IRB a proposal to conduct similar research in a larger and more geographically and ethnically diverse sample. This proposal was also approved by the IRB and was submitted to and approved by NIH. NIH did not raise any objections regarding human subject safeguards.

Recruitment into the larger study was initiated by a letter mailed by the investigators to all families, regardless of race, after the older sibling's case had been adjudicated. If the parents and child were interested, the study was explained in detail and, if the parents consented and the child agreed, the family was enrolled. Only families who had participated in the larger study were considered for the fenfluramine study. Families were told that a related study was underway and asked if they might be interested. If they were, they were referred to the lead investigator who explained the study in detail. The consent process occurred over several visits and, again, children participated only if both parents and children agreed to the procedures at all times. Families were specifically told that participation would not influence any court or correctional decisions. At the time of selection, all of the older siblings had already been adjudicated.

In the fenfluramine study, a small dose of fenfluramine was given in the form of a single, oral tablet, an amount that has always been judged safe. Nevertheless, the IRB conservatively designated the study as research "involving no more than a minor increase over minimal risk," that is, a low level of risk. The IRB sought information to confirm the safety of the single dose of fenfluramine in children before permitting the study.

Although the IRB determined that the study provided no direct benefit to the individual participants, it was anticipated that the children would receive a number of indirect benefits–and they did. The children received expert neuropsychological, general and mental-health evaluations. Findings from these evaluations led to referrals for visual, dental and pediatric care

and, in the case of children with educational problems, were used to expedite appropriate educational assistance. Eighty-five percent of the families continued to attend the research clinic for the four years covered by the study, suggesting that the mothers and children found the study a helpful and positive experience. The study provided important information for developing prevention and treatment strategies for children with antisocial behavior. It helped provide a foundation for a new approach to help parents raise children who are at risk for behavioral problems. Studies to examine the utility of these interventions are now underway with federal support, including a recent grant from the Department of Education.

This is the goal of research – to lead to the development of effective services and treatments.

Again, we appreciate the opportunity to testify at this hearing and would be happy to respond to any inquiries.

UNITED STATES HOUSE OF REPRESENTATIVES
COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT
SUBCOMMITTEE ON HUMAN RESOURCES
JUNE 11, 1998 HEARING
"INSTITUTIONAL REVIEW BOARDS: A SYSTEM IN JEOPARDY?"

Written Testimony of

B. Timothy Walsh, M.D.
Co-Chair, New York Psychiatric Institute Institutional Review Board, 1990-1997
Psychiatrist, New York Psychiatric Institute
Professor of Psychiatry, College of Physicians & Surgeons, Columbia University

John M. Oldham, M.D.
Director, New York Psychiatric Institute
Professor of Clinical Psychiatry, College of Physicians & Surgeons, Columbia University

Overview of the Research and the IRB Review

The research study which we have been asked to discuss was focused on violence and antisocial behavior among youth. The recent deadly shootings at schools across our country and the rising tide of youth suicide are tragic reminders that we must do more to understand and to prevent violence among young people. The purpose of the study conducted at New York Psychiatric Institute (NYPI) was to learn more about the origins of troubled behavior among young people, in particular, the development of antisocial behavior. At present, no effective treatment exists for such behavior, and the broad goal of the project was to identify factors–psychological, environmental, and biological–which increase a child's risk of developing such problems. The hope was that, if successful, this research would lead to targeted interventions to help prevent these difficulties from developing in youngsters at risk.

After receiving the investigators' initial application, the NYPI Institutional Review Board (IRB) requested additional materials to evaluate both the scientific merits of the study and the

potential risks and benefits to subjects. These issues were carefully considered, as was the process of seeking consent from and providing information to the participants and their families. During its review, the IRB applied the governing federal regulations as well as the underlying ethical principles. Time does not permit a comprehensive discussion of all the issues involved, but we have previously provided the Subcommittee with extensive documentation which was submitted to the Department of Health and Human Services' Office for Protection from Research Risks.

Who Participated

The fenfluramine study was one component of a larger, foundation-funded project which involved 126 boys with an older brother who had been adjudicated a juvenile delinquent. The investigators provided the IRB with strong scientific evidence that such younger brothers were at significant risk for the development of antisocial behaviors. The study of risk factors is important in many fields of medicine. For example, individuals in families at high risk for heart disease may be studied to determine how factors such as elevated cholesterol contribute to the later development of the heart disease. The investigators believed that a study of youngsters at risk for developing antisocial behavior would increase understanding of the factors that contribute to this problem, and thereby provide leads toward interventions to prevent it. The IRB was convinced that the proposed study had scientific merit.

Because the research involved numerous meetings with these families over several years, the investigators sought potential participants living in proximity to NYPI. Officials of the Family Courts of Manhattan and the Bronx provided information on eligible families from the court records, in accordance with New York law. The overwhelming majority of individuals in this

court system and, therefore, the overwhelming majority of participants in these studies were from minority ethnic groups, primarily African-American and Hispanic. The investigators recognized that such work should be broadly based, and this study was the first phase of a larger research plan. Consistent with this plan, the investigators subsequently submitted to the IRB a proposal to conduct similar research in a larger and more geographically and ethnically diverse sample. This proposal was also approved by the IRB, and was submitted to and reviewed by NIH, but not funded, with no criticism whatsoever of the human subjects safeguards.

Benefits to Participants

It was hoped that this study would result in new knowledge about identifying youngsters at highest risk for developing antisocial behavior and about ways to prevent the development of this behavior. Although the study was not primarily designed to provide direct benefit to the participants, it was anticipated that each child would receive a number of indirect benefits, including comprehensive medical and neuropsychological evaluations designed to detect learning, emotional or medical problems. When problems were detected, families were assisted in obtaining appropriate services. For example, a serious heart problem was discovered in one child, and the family of another sought help from the research staff for a child who was dealing with his father's suicide.

The Consent Process

Recruitment into the larger study was initiated by a letter mailed by the investigators to the families. If the parents and child were interested, the study was explained in detail and consent was obtained. Only families who had participated in the larger study were considered for

the fenfluramine study, on which we are focusing today. Families were told that a related study was underway, and asked if they might be interested. If they were, they were referred to the lead investigator who explained the study in detail. The consent process occurred over several visits, and children participated only if both parents and children fully agreed to the procedure at all times. If a parent expressed interest but a child did not, the child did not undergo the procedure. For example, those children who objected to having their blood drawn did not participate. As is customary in research studies of this type, participants were compensated for their time (6 to 8 hours, including transportation) and effort; parents were given $100, and children were given a $25 gift certificate.

The Use of Fenfluramine

A large body of scientific evidence suggests that the brain chemical serotonin plays an important role in the regulation of violent behavior, both outwardly directed, such as aggression, and inwardly directed, such as suicide. The investigators were interested in obtaining a measure of brain serotonin function in these youngsters, and, since brain serotonin cannot be measured directly, proposed to give subjects a single oral dose of the medication fenfluramine. By measuring changes in the level of hormones in the blood after fenfluramine, the investigators could obtain an indirect measure of brain serotonin function. An analogy might be the glucose tolerance test: a dose of glucose is given to individuals at risk for diabetes, and blood sugar levels are measured as an indication of the body's release of insulin.

At the time this study was proposed, fenfluramine had been marketed as Pondimin for over twenty years for the treatment of obesity. The NYPI IRB, which included a pediatric neurologist, carefully reviewed the potential risks of fenfluramine known at that time, and

obtained information from other investigators who were familiar with its use in children. After a thorough and lengthy review, the IRB concluded that the use of fenfluramine in this study entailed "no more than a minor increase over minimal risk" and therefore could be conducted under the applicable federal regulations governing research with children. Fenfluramine studies were carried out in 36 youngsters, and, to the best of our knowledge, none experienced significant problems.

Concern about the use of fenfluramine has subsequently developed because of the association between the use of fenfluramine, marketed as Redux, and the development of heart valve abnormalities. It may therefore be useful to review some additional information about fenfluramine. First, concerns about valvular damage emerged in 1997, well after the IRB's review and the conclusion of the NYPI study in 1995. Second, the data which have emerged suggest that valve damage occurs in a fraction of obese individuals who took fenfluramine for months, often in combination with another medication, phentermine. There are no data of which we are aware suggesting that a single, low dose of fenfluramine alone, as used in this study, is associated with any risk of cardiac damage. In fact, even after fenfluramine was withdrawn from the market for the treatment of obesity, the FDA has continued to permit the use of a single dose of fenfluramine in research studies. Finally, researchers outside of NYPI have described experience with more than 1,000 research subjects, including over 200 children and adolescents, who have participated in fenfluramine studies. All of these studies were presumably approved by the relevant IRB's, and many or most were conducted with support from NIH, which carries out a separate ethics review. The widespread use of fenfluramine in these research studies supports the view, taken by the NYPI IRB, that this procedure was of low risk.

The Research Findings

This study provided important information for developing prevention and treatment strategies for children with anti-social behavior. First, it demonstrated that the relationship between behavior and brain chemistry may change during development. While nerve cells which use serotonin appear to be underactive in certain adult psychiatric illnesses, the opposite (overactivity) may occur in certain child psychiatric disorders. Second, the researchers found that this difference may relate to the rearing environment. Children who were reared in nurturing environments generally had serotonin levels associated with lower levels of aggressive behavior.

These findings emphasize the potential importance of early interventions to prevent the development of problems in young people. For example, the results of the study suggest that some forms of treatment might not only help behavioral problems, but also prevent changes in the chemistry of the brain which may make later treatment more difficult. Moreover, by describing the link between nurturing behavior and serotonin, the study may ultimately allow us to understand those aspects of the parent-child relationship that are most protective against the development of antisocial behavior.

The importance of the published results of this fenfluramine research was recognized in an editorial in a leading medical journal and by the American Academy of Child and Adolescent Psychiatry.

In closing, we would emphasize our belief that research on the development and prevention of violent behavior among young people is critical for our country. Studies on this sensitive topic must be carried out with the strictest attention to safeguards for the research

participants. In the study under consideration today, the NYPI IRB carefully applied the federal regulations governing research and the ethical principles on which they are based.

DEPARTMENT OF HEALTH & HUMAN SERVICES

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June 8, 1999

Stewart O. Hughes
Managing Director
Research Foundation for Mental Hygiene, Inc.
44 Holland Avenue
Albany, New York 12229

James L. Stone
Commissioner
New York State Office of Mental Hygiene
44 Holland Avenue
Albany, New York 12229

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1376
Research Projects: "Neuroendocrine Response to Fenfluramine Challenge in Boys" and "Platelet Serotonin 2A (5-HT2A) Receptor Characteristics and Parenting Factors for Boys at Risk for Delinquency: A Preliminary Report"
Principal Investigator: Dr. Daniel Pine

Dear Mr. Hughes and Mr. Stone:

The Office for Protection from Research Risks (OPRR) has reviewed all prior correspondence between OPRR and the Research Foundation for Mental Hygiene (RFMH) regarding the above referenced research activities. In addition, as you know, on March 3, 1999, OPRR conducted a compliance oversight site visit at the New York State Psychiatric Institute (NYPI) in order to evaluate these research activities. The evaluation, conducted by 6 OPRR staff with the assistance of 3 consultants, included meetings with institutional officials, the former and current Institutional Review Board (IRB) Chairpersons, over 20 IRB members, IRB administrative staff, and Dr. Daniel Pine and two of his co-investigators for this research.

Based upon this evaluation, OPRR makes the following determinations relative to protections for human subjects in these research activities:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR Part 46, Subpart D, require additional protections for children involved as subjects in research.

OPRR finds that the NYPI IRB was clearly cognizant of the requirements of 45 CFR Part 46, Subpart D, when conducting initial and continuing review of this research.

(2) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. Based upon discussions with IRB Chairs, IRB members, and the investigators and its review of IRB documents, OPRR finds that the NYPI IRB consistently made and documented these required findings when reviewing this research.

(3) For the fenfluramine challenge studies involving children, OPRR finds that the NYPI IRB determined that this research involved greater than minimal risk and no prospect of direct benefit to individual subjects, but was likely to yield generalizable knowledge about the subject's disorder or condition. OPRR further finds that prior to approving the research, the IRB made and documented the following four findings required by HHS regulations at 45 CFR 46.406:

(a) The risk represented a minor increase over minimal risk.

(b) The procedure presented experiences to subjects that were reasonably commensurate with those inherent in their actual or expected medical, dental, social, or educational situations.

(c) The procedure was likely to yield generalizable knowledge about the subjects condition which is of vital importance for the understanding or amelioration of the subjects' condition.

(d) Adequate provisions were made for soliciting the assent of children and permission of the parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

(4) Based upon findings (1)-(3) above, OPRR finds that this HHS-supported research was conducted in accordance with the requirements of 45 CFR Part 46, Subpart D.

Based upon its discussions with the IRB Chairpersons, IRB members, and institutional officials, OPRR makes the following determinations regarding the current NYPI IRB:

(5) OPRR finds that the IRB Chairperson and members appear to have a detailed understanding of the specific requirements of the HHS humans subjects regulations at 45 CFR Part 46. OPRR further finds that the IRB Chairperson and members are enthusiastic and dedicated to the protection of human subjects.

(6) OPRR finds that the IRB membership has the diversity, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects, as required under HHS regulations at 45 CFR 46.107(a).

(7) OPRR finds that the NYPI IRB regularly reviews research involving vulnerable categories of subjects, including children and mentally disabled persons.

(a) HHS regulations at 45 CFR 46.107(a) require that an IRB which regularly reviews research involving a vulnerable category of subjects consider inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects. OPRR finds that the IRB membership includes more than one such individual for each of these vulnerable categories of subjects.

(b) HHS regulations at 45 CFR 46.111(b) require the IRB to ensure that additional safeguards have been included in research to protect the rights and welfare of vulnerable subjects. OPRR finds that IRB has established procedures for ensuring that such safeguards are included in research involving vulnerable subjects.

As a result of the above findings, there should be no need for further involvement of OPRR in this matter. Of course, OPRR must be notified should new information be identified which might alter this determination.

OPRR appreciates the continued commitment of RFMH and NYPI to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Sanford Leikin, M.D.
Medical Compliance Officer
Compliance Oversight Branch
Division of Human Subject Protections

Michael A. Carome, M.D.
Chief
Compliance Oversight Branch
Division of Human Subject Protections

cc: Ms. Susan J. Delano, RFMH
Dr. John D. Rainer, NYPI
Dr. Daniel S. Pine, NYPI
Dr. John M. Oldham, NYPI
Dr. Gary B. Ellis, OPRR
Dr. Melody H. Lin, OPRR
Ms. Michele Russell-Einhorn, OPRR
Dr. J. Thomas Puglisi, OPRR
Dr. Clifford C. Scharke, OPRR
Dr. Katherine Duncan, OPRR
Ms. Freda Yoder, OPRR

Mr. MICA. Thank you, and I thank each of our witnesses and our first panel, and what I'd like to do now is begin a series of questions and I'll yield to ranking member this morning, Mr. Towns.

Obviously, there's an incredible explosion of research, probably beyond anything we could have imagined even a decade ago. And it's important that we move that research forward and human beings benefit by that process. As we heard from our witnesses, we have a system to deal with this in regulations to protect people that were developed some two and a half decades ago. There's a system somewhat convoluted in its structure, and antiquated, but progressing with the rapid advances we're making today and the sheer scope of research that's being conducted. The purpose of this hearing is to try to sort through the maze and there are many, many questions and aspects for all of us.

I'd like to start today by asking the Inspector General, I read through all the testimony of the past hearing, and there was another hearing before this. You came today and said the system is badly in need of reform. There are many aspects of that reform. Let me deal first with structural aspects.

The Secretary has moved OPRR from NIH to the Secretary's office. Is that sufficient structural change to deal, again, with the administration, the oversight, and the management of this whole order, or do we need other structural changes that have not been put in place? Let's deal with the structure first.

Mr. YESSIAN. Mr. Chairman, we haven't focused on organizational structure. If the human subject protection function gains some independence and visibility that would seem to be desireable. But our position has been that that isn't an issue for us to address in any detail, and that there are basic issues that go much beyond structure.

The basic reforms remain to be carried out. They have to do with the nature of oversight, the kind of educational mandates, if and how we change any of the regulations, what happens at the IRB level. There's still a full agenda there.

Mr. MICA. The second question would be if you have identified any legislative changes that may be necessary to deal with the overall structure, and do you have any recommendations dealing with legislation that may be required either for structural changes or processes?

Mr. YESSIAN. I think a number of our recommendations could be enhanced by legislative changes. It's possible in some cases they could be done administratively as well. But on call for a mandate that there be a registration of all IRBs would probably take legislation.

Mr. MICA. That cannot be done by rule?

Mr. YESSIAN. I defer to Dr. Ellis on that.

Mr. MICA. Dr. Ellis, can that be done by rule?

Mr. ELLIS. The current regulations and statutes I think would permit registration of a large portion of the institutional review boards in the United States, but there are some that just simply fall outside of our current statutes.

Mr. MICA. So you would need additional statutory authority to bring everyone into the fold, is that what you're saying?

Mr. ELLIS. For instance, currently OPRR has the name and address of every institutional review board within our authority. This registration not a problem for OPRR, I think it's an opening question for FDA, but even a combination of OPRR and FDA and their overlapping jurisdictions wouldn't reach a completely private institutional review board that doesn't engage in FDA regulated research, for example. Couldn't get every last one from where we stand right now.

Mr. MICA. Back, if I may, to the Inspector General.

The first hearing contained a substantial number of recommendations. Now, first of all, the Inspector General, your report had offered a number of recommendations. What percentage of your recommendations have been instituted; 10 percent; 8 percent; 5 percent performed?

Mr. YESSIAN. Probably 5 to 10 percent. The most significant response is the enhanced enforcement effort from the Office of Protection from Research Risks.

Mr. MICA. And you did cite whether there were some instances of changes in procedures?

Mr. YESSIAN. But much remains to be done. A few highly visible enforcement efforts, by the way, have a lot of reverberations. Some have said, some of those efforts are like the nuclear bomb of enforcement. Many have sort of said there but for the grace of God go I, after they went into Duke University, so there has been some positive reverberations there.

Mr. MICA. But you're saying 5 to 10 percent actually——

Mr. YESSIAN. I would say so.

Mr. MICA. Dr. Lawrence, the Inspector General has made recommendations at this last hearing, the hearing that was conducted June 11, 1998, from some pretty substantial organizations; the Center For Biomedical Ethics offered recommendations. The American Association for Medical Ethics and the American Psychiatric Association offered recommendations. I read through some of these recommendations. Some of them are very similar to what the Inspector General has offered.

These were recommended almost a year and a half ago. The National Bioethics Advisory Commission report was a year old. Why has there been such a delay in implementing the recommendations by the Department?

Dr. LAWRENCE. Mr. Mica, I have no way of calculating percentages on this, I'll start by saying that.

Mr. MICA. We can go over each of these one at a time. It appears that one or two minor changes or recommendations were instituted by the Department. Our responsibility in an oversight capacity is to find out, what's the holdup?

Dr. LAWRENCE. Let me say this: The OPRR did move to increase its enforcement activities, and I think that the IG has underscored that. In response to the NBAC report that referred to human subjects with impaired capacities, while there is not a regulatory change, there are a set of NIH-issued guidelines that address many of the particular areas that the impact report pointed up.

Third thing is that OPRR moved very, very aggressively in its educational forum to put more and more information on to the Internet so that those individuals who needed it most could be able

to refer to, had it available, and also that patients had it available to take a look at to see what it is that they should be expecting.

Now, let me add something about the structural change, for a moment, if I may. The structural change from NIH to OS, I think is very significant. Will the structural change itself make a difference? No. It's what the Secretary and what Dr. Satcher wishes to do with it. The structural change moves OPRR into a position where it will focus solely on human subjects protections. The office in OS will also have an increased capacity to have sway over the agencies within the Public Health Service that do fund services, making it much easier to communicate and it also makes it easier to communicate on a chief officer, as in Secretary to Secretary level with the other signatories to the common rule. So I think there are things that are currently moving.

Now, let me give you a prognostication. OPRR is working assiduously on looking at the streamlining of assurances. We're almost there, I can't say that we are there. I would say that probably within the next 120 days OPRR will be in a position to directly respond by the simplification of the process without compromising patient safety.

Mr. MICA. Let me ask you, Dr. Lawrence; I guess structurally and from an oversight standpoint, IRBs that receive Federal funds or projects that receive Federal funds that have IRBs, OK. It would be a given that we would want to make certain proper procedures and reforms are in place with that group, is that correct?

Dr. LAWRENCE. Yes, sir.

Mr. MICA. OK. Now, your colleague, Dr. Ellis, has said that there's a larger universe out there, and there are many research activities that don't receive Federal funds. Is it the Department's position that all of these should be covered?

Dr. LAWRENCE. We believe very strongly that all participants in human subjects research should be afforded the maximal protections possible. We urge those groups that are not part of our funding, of course, to adopt our own approach to things. Where there is an MPA, a multiple project assurance, the institution signing that MPA actually pledges its entire research portfolio, as I recall——

Mr. ELLIS. Essentially, 98 percent——

Mr. MICA. Dr. Ellis.

Mr. ELLIS. Thank you. Essentially 98 percent of the major biomedical research institutions that have a multiple project assurance, that's an umbrella agreement with our office, voluntarily pledged all their activities irrespective of funding to our rules. So that's one way we've been able by jawboning, I guess, to extend the coverage as far as we possibly can.

Mr. MICA. Dr. Lawrence, so it is the intent of the Department to include all of those participating in human research projects, experimental projects, to come under an umbrella?

Dr. LAWRENCE. We are currently operating a work group that takes a look at both FDA and OPRR human subjects protections activities to see where the overlaps are, where the gaps are.

Mr. MICA. Now, Dr. Ellis testified that he did not believe that you had statutory authority to really include this other group that does not receive Federal funds and regulate them, and it would re-

quire, I don't want to take anything out of context, but it might require legislative change.

Dr. LAWRENCE. Yes, sir.

Mr. MICA. Is the Department preparing anything for Congress for legislative change or to expand that authority?

Dr. LAWRENCE. The President has asked the National Bioethics Advisory Committee to take a very, very broad based look at this.

Mr. MICA. Now, we've heard Dr. Cassell say that well, they've produced this document, but he said that in the research area, I believe he said it was going to be 6 more months before they complete their study and recommendations. Dr. Cassell, is that correct?

Dr. CASSELL. Yes. That's the goal. The goal is that comprehensive recommendations about the protection of human subjects, and it will be probably 6 or more months before those are finished. However, what is presently in the report that you have in your hands, if those recommendations were implemented, we would have already gone a large step forward.

Mr. MICA. Now, how many of the recommendations contained in this December 1998 report have been instituted?

Dr. CASSELL. I think zero is probably an accurate number.

Mr. MICA. So we're 5 to 10 percent with the IG and we're zero in this, and you're telling the subcommittee this morning that because there has not been action on your report, that has, in fact, delayed the next step in your process, is that correct?

Dr. CASSELL. Oh, yes, and I agree with the Inspector General, what they recommended would move the whole process forward. There's considerable inertia in making things happen.

Mr. MICA. So let's go back to the Department. How does the Department respond to not taking action on 90 to 95 percent of IG's recommendations, and zero percent of these recommendations, and delaying the process to where we do not have any of these protocols, procedures, regulatory assurances in place? Dr. Lawrence.

Dr. LAWRENCE. As I said, Mr. Mica, subject to that report, OPRR did take a very, very careful look, especially at the impaired participants section and they did take action. The second thing is that I think that we are in a position where structurally, and inside the Department, we want to be as careful as we can. We have to keep in mind when we take these steps, that there is also a potential for doing things wrong. We prefer to take very thoughtful, deliberative steps.

I do take exception to the characterization that so little was done by the Department. I have outlined for the committee those things that were done as the result of the IG's report. Is it 100 percent? No, sir.

I also think that the substantive steps that NIH took to produce guidance, specific guidance in response to NBAC to protect those individuals who are impaired were substantial. Have we done 100 percent? No, sir, and that's why the secretary has decided to move forward and to reorganize OPRR into OS, to give it a higher level of visibility, to give it a higher level of flexibility and also to start working on the actual activities to protect human subjects.

Mr. MICA. My next area of concern would be individuals who are in a situation where they're not able to really make a decision, whether they be mentally ill, retarded, or children, and you're tell-

ing me that some changes in procedures have been made, then today's paper cites the case of this young man, who just turned 18, Jessie Gelsinger, and I guess your Department has said he should have been eligible for this, and then found out that the informed consent form that investigators gave patients deviated from the one the agency had approved.

So I have concerns that while some of these procedures to protect children, to protect others who may not be able to make informed decisions, you're saying changes have been made and today's newspaper cites, maybe it's just one case but it appears that some of the protections, in any event, and changes have not been instituted.

How would you respond?

Dr. LAWRENCE. As to your reading the article, Mr. Mica, as it turns out, I was kind of ticking off some things here in taking notes. First off, let me say that the death of anyone or the injury of anyone is truly a regrettable event. And that's what we're all trying to protect.

Now, in this case, I think if we reread the article again, what we would find is that had that investigator followed the existing requirements, that there would have been informed consent. So it seems to me that if this article was true, and I have no specific knowledge, that if there is an issue here, OPRR's regulations and guidance cover all of these areas. That's my answer, sir.

Mr. MICA. Well, what concerned me when I read this report is one of the matters in which some of these IRBs proceed in and I can't find the passage, I thought I had it marked here. It said the way the IRB proceeded was if the patient, if some of the patients hadn't died, then they would proceed, and that, they tried it on a few, and if some didn't die, that would be the criteria for proceeding.

I was a little bit concerned that some of the recommendations that had been made by almost every group relating to educational assistance of the IRB people who served has not been put into place. I was concerned a little bit about the representation on the Board, nothing in that area has been put into place that I know of, a requirement there. What also concerns me are the reports that some people who serve on these Boards, and they may be federally funded, may be receiving payments or some type of funds from pharmaceutical companies that have an interest in that particular research or the product that's being applicated by them. Where are we with those matters?

Dr. LAWRENCE. I will answer part of that and ask Dr. Ellis to address part of the question about financial disclosures.

Let me say a couple of things about education. Education is very important. NBAC has said it, everyone has said it. As we move forward in the restructuring of OPRR, we are going to be looking very carefully at how the current resources are being distributed. I think the strategy, Mr. Mica, that we're going to be using as we move forward with advancing OPRR and its ability to protect human subjects, to use the current phrase, is to pick the low hanging fruit. There are some things that we can do right now, there are things that we can do very, very quickly, not the least of which is to have an oversight and advisory board that is totally independ-

ent, where we can ask this kind of question, where we can go to this board and say what are the priorities.

I think one of the important things in seeking to improve human subjects protections is we have to keep asking questions, because the target, quite frankly, sir, keeps moving.

So I think that many of the recommendations that are in each of these reports, if not having been addressed in specifics, they're going to be addressed through the process of conversation with that advisory committee.

Mr. MICA. Let me ask you this: Some of these things——

Dr. LAWRENCE. Would you like to have——

Mr. MICA. We'll get to Dr. Ellis on the disclosure and conflict of interest.

Dr. LAWRENCE. Sure.

Mr. MICA. But I come from a pretty conservative side of the spectrum. I don't like additional government regulations and red tape and bureaucracies. Has the Secretary or OPRR or any of these agencies sent out an advisory memo to—Dr. Ellis, didn't you tell me we could identify the IRBs that are getting Federal money?

Mr. ELLIS. That's correct.

Mr. MICA. We can identify them. Have we sent out a simple advisory statement or recommended procedure asking them to address peer education, broader representation disclosure, or conflict of interest? Has any of the overseeing agencies involved sent out anything on this since the last hearing?

Mr. ELLIS. Well, the answer is emphatically yes.

Mr. MICA. Can you produce copies of those for the record and the subcommittee, please?

Mr. ELLIS. Certainly.

Mr. MICA. OK. In all of the areas or some of the areas?

Mr. ELLIS. Probably the single best integrated advice went to the 240,000 subscribers of the Journal of the American Medical Association November 24, 1999 where I wrote an editorial titled "Keeping Research Subjects Out of Harm's Way." The main point of that was education, education, and education. I'll be glad to supply that and others.

Mr. MICA. Has the Department sent an advisory notice or specific guidelines or recommendation to the IRBs outlining maybe what was in your probably excellent editorial comment?

Mr. ELLIS. You're too kind. We have addressed institutions and their IRBs directly by first class mail through the years with a 1993 edition of an IRB guidebook.

Mr. MICA. My question dealt with since the last hearing, can you produce for the committee your advisory notices in any or all of these areas?

Mr. ELLIS. Sure. Let me submit for the record everything we've produced since June 11, 1998. I'll be glad to do it.

Mr. MICA. Great, that would be excellent.

Now, Dr. Ellis, if you could tell us about our addressing the problem of disclosure and conflict of interest, then I'll go to Mr. Towns. I have more questions, Mr. Towns, but I'll——

Mr. TOWNS. Go right ahead.

Mr. MICA. Since we've gotten into this, I appreciate your patience. Go ahead, Dr. Ellis.

Mr. ELLIS. Mr. Chairman, this issue of the flow of money through human research is 1 of the 10 most frequently asked questions, 1 of the 10 most frequently discussed topics and there are two issues. One is payment to research subjects, but I think you're most interested now in payment to investigators, or a variant of that—conflicting financial interests of IRB members as they review research.

The Department's human subject regulations get at this only peripherally. There's one very direct clause that says no voting IRB member may have a conflicting interest in the research put before that Board, and we see the widespread practice of recusal when a voting IRB member sees something that could be a conflict. A conflict many times is intellectual or academic, a collaborator's proposal, but it can be financial.

Now, that's the strongest hold that the regulations have on this, and it is admittedly weak. The only other portion of the regulations that I can see that pertains to this is instruction that informed consent from a subject shall only be sought under circumstances that minimize the possibility of undue influence or coercion. My reading of that means that if the investigator is somehow reaping financial benefit, that the IRB has full entree to ask about all those circumstances, because the IRB has the absolute mandate to minimize the possibility of coercion or undue influence on the subject that the investigator is recruiting. Those are the two places I see it in the human subject regulations.

This is something that's going to have to be addressed at the national level, and my guess is will eventuate in some additional detailed guidance, if not regulation, because it's a very important topic and a current topic.

Mr. MICA. I see that the Inspector General wanted to respond. I would be interested—again, we want to insure that protections are there, particularly in this conflict area with IRB members. We don't want to dissuade people from serving and getting into all kinds of complicated disclosure mechanisms. That can be a deterrent to having people who are highly qualified participate. If you would.

Mr. YESSIAN. Yes, Mr. Chairman. I wanted to comment on this, because since the last hearing, most of our work in this area has been on the issue of recruitment and industry sponsored trials and I have to say conflicts are just inherent in this process. They apply where there's a government grant as well as in industry trials, but it's important to emphasize how at the IRB level, at the ground up, how the environment is really turning into much more of a marketplace environment, and some major research institutions, one of the IRBs I just talked to, one of the best teaching centers in the United States has half of their proposals now come from industry sponsored research.

This raises all kinds of questions and there's very little guidance that the IRBs have and they don't often know where to turn when it comes to OK, what's appropriate here, Dr. Ellis touched it. Are there circumstances in which informed consent is being provided, being tarnished in some way in is there coercion here, maybe unintentional. Is it really voluntary? Is confidentiality being broached if somebody is being called about participating in a project because

of, without their, without their knowledge that their records are being accessed?

These issues are really stirring up at the IRB and institutional level, and it's for this kind of reason in a way, notwithstanding the fact that some progress has been made, at the Federal level in addressing some of these issues, at the ground level in a way, the problems are extenuating even faster than our progress is, because it's not static there, it's a rapidly changing marketplace.

Mr. MICA. Thank you, I'll probably go a second round. Mr. Towns, you're recognized.

Mr. TOWNS. Thank you very much, Mr. Chairman. I want to point out this is a very important area to discuss, because we're talking about protecting people and I think based on that would be the New York Times article today, and of course the Washington Post yesterday, you know, we have some very serious problems.

Let me begin by saying first, Dr. Lawrence, when will the move of the OPRR be complete?

Dr. LAWRENCE. We are targeting March 2000.

Mr. TOWNS. And how will this move improve the protection of human beings who are subject to biomedical research?

Dr. LAWRENCE. Well, first off, Mr. Towns, I think it's important to have an office that focuses solely on human subjects. This is not to say that animal welfare protection is not important, they are, but to have a staff that focuses very, very specifically on the issue, I think is of great value.

The second thing is having the cachet of having the office located in the Office of the Secretary, and the ability of the secretary to speak out on these issues, supported by her own staff, which is very, very important.

The third thing is that I believe we will find communications inside the Department and intra departmentally improve significantly with the office on that level. How this translates exactly to human subjects protections, I cannot give you a number or a value. However, I do believe that it is a major step forward in what needs to be a sequence of events, including the appointment of the advisory committee that will then be able to identify the very, very specific solid steps that need to be taken to move forward.

Mr. TOWNS. Have you consulted the Office of Personnel Management about the necessity to change Director of OPRR or to the position with the Senior Executive Service?

Dr. LAWRENCE. Our administrative division, which is Assistant Secretary for Management and Budget now has all that paperwork and they are responsible for the interface with other agencies. I have no specific knowledge of exactly where it sits at the moment, sir.

Mr. TOWNS. Right. So actually I can assume from that statement, no. That was a no, wasn't it?

Dr. LAWRENCE. I have no knowledge of exactly where it is, so I can't say yes or no.

Mr. TOWNS. So, then, I think we could say no. Maybe you don't have yes or no, I think we could be on the safe side and say no, OK? I don't want to—I think we can do that, no.

Dr. LAWRENCE. Yes.

Mr. TOWNS. I think when we move forward we don't forget about the fact that the Inspector General noted that last year OPRR has moved, improved and of course had been much more aggressive in conducting site visits and elevating the importance of protecting human subjects. I think that's important. So while I support the plan to move the office over to NIH, and some people, you know, feel that based on the fact that some folks have been very aggressive in doing things, they will not be rewarded, but they will be penalized, and I'm hoping that we don't see that in this particular instance. I'm talking about Dr. Ellis, who has done research in terms of, and written in terms of articles about harm's way, so I just want to pass that along, because there's rumors floating everywhere, which has nothing to do with anything, I'm sure, but I just sort of wanted to make that comment on the chance we had to have this exchange.

Dr. LAWRENCE. Thank you, sir.

Mr. TOWNS. Let me move forward. First of all, I want to ask the general question to any of you, how many IRBs do we have out there? Anybody know? How many IRBs are there?

Mr. SHAMOO. Around 5,000.

Mr. TOWNS. I wish I could accept your answer, I wish it was true and all that, but anybody at the table here, if you could tell me how many we have. Yes, Dr. Ellis.

Mr. ELLIS. We have estimated there's some 3,500 to 5,000 IRBs in the United States. It's not really possible to give a more precise estimate.

Mr. TOWNS. 3,500 to 5,000. Anyone else want to give me a number? Or you don't know? That's my problem. Even the person that knows is saying 3,500 to 5,000, there's 1,500 in there we're not certain about, and I think that's the real issue here today. I think that we need to some way or another come up with a way to know what's out there. I think that's the first thing, so—let me just move to one of the things that sort of keeps me involved in this in a very serious way. I want to let you know that I'm not going to go away on this one, I'm going to stick with it. I'm going to be here, you need to know this, I make it clear, it's not somebody who will come in, say something and then move on.

Let me begin by asking you, Dr. Cassell, the fenfluramine study was that a central, valid piece of research based on your many years of professional work?

Dr. CASSELL. Well, I tell you, it's not for me to decide that. It's not within my competence, but I'll tell you what is important, that we heard testimony about that research in July 1997. It is research like that, whether valid or not, that raised issues of the protection of human subjects, and my own belief is, if we were talking 5 years from now, it would have more difficulty getting passed an IRB than it had now. I don't question for a moment the expertise of the people that did that research, it's their line of work, they're good people. I don't question the validity of the hypotheses that went into it, that's their work, and I believe they're correct, that isn't really the issue.

There are a lot of good studies that people would like to do that will move science forward and so forth, but that's not the only value present. Progress isn't the only value. The protection of

human subjects, the care of people who cannot take care or protect themselves, ranks as high or higher than scientific progress and that's really what we're talking about.

Mr. TOWNS. Thank you very much. I couldn't agree with you more.

Let me just go to you, Dr. Walsh. In your testimony, it was June 1998, before the committee, subcommittee, you said that all of the participants in the New York Psychiatric Institute fenfluramine research involving children were not members of minority groups.

Dr. WALSH. If that's in the testimony, sir, that's an error. All of the members of the fenfluramine challenge study were members of minority groups.

Mr. TOWNS. It's in the record. In fact, I want to be honest with you, I read it four times.

Dr. WALSH. It is then my error, for which I apologize, if I failed to correct the record. Certainly there was no attempt to say that, in the fenfluramine study, the children were not African American.

Mr. TOWNS. Let me give it to you, to correct the record, I think we should. What was the breakdown?

Dr. WALSH. I'd have to look at the paper, sir. If you want accurate information, I'll have to look through my papers.

Mr. TOWNS. Also in Dr. Oldham's testimony, he said that race was not an issue here. You mean to say by happenstance or coincidence, it just happened that everybody was minority?

Dr. WALSH. Yes, sir.

Mr. TOWNS. That's a strange coincidence.

Dr. WALSH. Let me explain. Here's how the recruitment occurred. These investigators were interested in finding out ways to help families, help parents raise their kids in a difficult environment. They focused on the development of antisocial behavior and proposed in their research to identify families who were involved in the family court systems of Manhattan and the Bronx, because they were in close geographical proximity to where our institution is. They were proposing to do was to conduct home visits and follow these families for 4 years.

It turns out that the overwhelming majority of families in these court systems are African American and Hispanic. In the study that was conducted, the overall study, I think the proportion of Caucasians are 2 or 3 percent, there are a few, but it's a very small number. But my understanding from the investigators is this is not different from the makeup of the Manhattan and Bronx family court systems.

Mr. TOWNS. Dr. Walsh, you're a dancer. I want you to know I'm not your partner, either. You're a dancer. You mean to say you could not find one white kid?

Dr. WALSH. No, sir, there were two or three Caucasians in the overall sample of 126 children.

Mr. TOWNS. But they ended up being blacks and Hispanics.

Dr. WALSH. Let's be careful to be clear. There was a broad study to look at factors that were related to the development of antisocial behavior among youth. It's well-established scientifically that one of the risk factors, one of the ways to identify kids at risk is to find kids with an older brother who has had some trouble, and that's the procedure that the researchers proposed. They chose to get

them, as was described, from the Bronx and Manhattan court systems.

People were recruited, families were recruited from that court system without regard for race or ethnicity. The investigators initially proposed to have an ethnic exclusion. The IRB did not permit it. We absolutely told them you cannot have ethnic exclusions in this research. Nonetheless, their final sample composition of 126 kids involved 3 Caucasians, and I am told, that that is a reasonable statistical reflection of the makeup of the families in the Bronx and Manhattan court systems.

Mr. TOWNS. Dr. Walsh, really, we've been down this road before, and of course, and I don't want you to have to correct the record again when we talk. I want you to know that this is a little different from what was said the last time, which would be how you arrived at getting them. So I don't know how you change, I mean, you're going to have to correct the record again evidently. Yes, Dr. Oldham.

Dr. OLDHAM. Congressman, let me clarify one thing I do not think is clear. Dr. Walsh described this as an initial overall sample of about 125 young boys. Of that 125, which did include a few nonminorities, there was a substudy of about 36. Those 36 boys were the 36 boys that participated in the fenfluramine study. Those 36 were entirely African American or Hispanic.

That was a completely random result of the volunteers who participated in the substudy, in other words, those 36 who agreed to participate in the substudy by coincidence did not include the very few who were in the entire sample, but when a statement is made that the sample did not exclude any subjects on the basis of race or ethnicity, that is correct.

Mr. TOWNS. Let me put it this way: Why don't we include Staten Island or Queens?

Dr. OLDHAM. This is actually the first——

Mr. TOWNS. It's part of the city, I figured you would look at the city.

Dr. OLDHAM. I think Dr. Walsh addressed part of that. We had a multi-phase design. This was step one of a multi- phase study and the second phase of the study was to move to other regions which would include other parts of the surrounding area, that would have included some other boroughs of New York as well as some other counties outside of New York City, which would have been a very different ethnic and racial distribution. This was actually submitted and approved by NIH as a followup study.

So we began actually where we had contacts already with the court systems that were adjacent to our exact location, which were the court systems of Manhattan and the Bronx, as a pilot to start the study. We didn't know until we received the information from those courts what the specific racial profiles would be of these groups.

Mr. TOWNS. I just want to ask you, before we move on, that's a strange coincidence that you had nobody, just black or Hispanic. That's a strange coincidence. Let me move on. I don't want to belabor that.

In your testimony, you note that the children involved in the study had behavior problems, yet you do not state that these so-

called behavior problems were the result of mental disorders. Was there ever a finding that all the children in this study had a specific mental disorder?

Dr. OLDHAM. Let me ask Dr. Walsh to comment on that. There were a number of types of problems that were identified.

Dr. WALSH. The majority of the children had symptoms of or met diagnostic criteria for mental disorders. At 1 year, in the overall sample, the number was I think about two-thirds. In the fenfluramine study to which you may be referring, it was about the same proportion, between two-thirds and three quarters of the subjects had behavioral problems, diagnosable behavioral problems.

Mr. TOWNS. Let me ask you about the study itself, fenfluramine. Some of these children were under 12.

Dr. WALSH. Yes, sir.

Mr. TOWNS. I think all of them were all under 12. Now, even in the research, the pharmaceutical company didn't have anybody under 12 involved in the research of the trials initially.

Now, they didn't have anybody, then you bring the youngsters in, and you use a drug on them that was not even tested in the trials with someone under 12. I mean, didn't that bother you?

Dr. WALSH. It's actually a common problem in pediatrics. Many drugs that are widely used for children, have not been specifically tested and approved by the FDA for use in children. I think that's recently been addressed or there's a change in the FDA approval procedure, but——

Mr. TOWNS. Let me interrupt you here. That's a drug that's going to benefit the kid, but in this situation it does not benefit them in any way.

Dr. WALSH. Yes, sir.

Mr. TOWNS. That's a difference.

Dr. WALSH. There was substantial data at the time in the literature about the use of fenfluramine in these very types of challenge tests in both children and adults prior to the initiation of the study at the Psychiatric Institute. There were thousands of adults and hundreds of children who prior to our approving this study, had participated in this kind of study without any significant risk or harm. And we determined that. We accessed that information, consulted with colleagues to try to determine that before the study was approved.

Mr. TOWNS. Even though they were not involved in the research initially, you still felt that somebody else had done it, now you can do it. I mean, is that your rationale?

Dr. WALSH. No——

Mr. TOWNS. I just want the record to reflect.

Dr. WALSH. I think this reflects what the job of the IRB is. An investigator has a proposal, a proposal that certainly involves unknowns. Questions that have not been answered to which there are no firm answers available. It's the job of the IRB to use its best judgment to evaluate what the risks of those procedures are.

I still believe we did a very conscientious job of doing so. We consulted with other people who did this kind of work, we looked at the literature, and we concluded, and it's a conclusion which I believe has not been seriously challenged: Fenfluramine used in the

way it was used in this study, even in youngsters, poses no significant harm.

Mr. TOWNS. Let me just say, I'm trying to move on. You stated in your testimony, Dr. Oldham, these children were at risk because they had a sibling who was in trouble with the law. Should everyone who has a sibling that's in trouble with the law be a candidate for biomedical research? If not, then what made these children candidates?

Dr. OLDHAM. Well, certainly that would be too broad a generalization to make, but there is a very good body of scientific evidence that younger brothers, not any children, not any siblings, but younger brothers of males who have been already identified as delinquents with antisocial behavior that is clear enough so that there has actually been an adjudication and a guilty finding and a decision by the court system, that children of these families, if there are younger brothers, are at increased risk to develop this kind of behavior, we feel this is an important, enormously critical problem, that needs to be studied. We do not at all feel that this is something that should be done without careful, careful thought, and studies like this need to be very, very seriously considered, both because of their importance, but because one has to guard against inappropriate research with inappropriate individuals.

However, if we feel that these younger brothers were in a category of high risk to develop similar problems and be on a course that would lead them to a very disturbed and difficult life course, if we could identify a way to intervene and to prevent some of this unfortunate outcome, we feel that this is very important.

I mentioned in my testimony the fact that there had been federally funded studies based on the methodology and the initial preliminary findings of these studies that are underway, funded both by NIH and by the Department of Education to try to involve prevention and avoidance of this unfortunate path by the youngsters.

Mr. TOWNS. Did you develop any treatment strategies?

Dr. OLDHAM. There were intervention and prevention strategies, that's what it would be at this point for these individuals, and they were referred for treatment in every case where there was a willingness on the part of the family to accept treatment and treatment was indicated because of diagnosed conditions that needed treatment.

Mr. TOWNS. Let me say that, you know, I'm trying to move on, but you know, I'm not sure that some of this is not society, poverty and all these kinds of things rather than being biological. I sort of raise that issue with you as well. Yes, Dr. Walsh?

Dr. WALSH. I agree with you, sir, very much, and that in fact was the point of the research. I want to underline, I appreciate your concern, sir, and I am very interested in your opinions and concerns about how we can better help people in our community. And I think we're an institution well known to be located in a minority community and I think we have an obligation to try to help the people who come to our hospital and live around us.

The problem is we have a lot of ignorance about what to do that would be helpful. A lot of the causes of some of the problems are social, environmental, economic, there's no doubt. But we're doctors and we try to find out ways that the medical and psychological pro-

fessions can help these people, and the only way that we can help break through the ignorance is through research. So we have to do research with these people—not on them, not to them, but with them, so we can get a better idea of what we might be able to do to help them, so that we can help them. And, sir, I strongly believe that that is what this study did.

The broad study identified things that parents were doing with their children that helped children avoid problems. And yes, it explicitly led to treatment studies that are now ongoing in the same community, in northern Manhattan, with, what I understand to be, the strong support of the local community, to help families living under difficult circumstances, help raise their kids the way we all want our kids to grow up.

So, sir, I understand your concerns. I deeply respect them, but I feel that we must continue to work with the community in which we live so we can help the people who come to us. I think it is our moral obligation.

Mr. TOWNS. Let me just go back to the IRBs. How should we structure them? Because we're hearing all kinds of things about conflicts, we've heard even corruption, lack of training, lack of qualifications, and I think that these are the things that we have to be concerned about, and the other part, you know, I'm not hearing any kind of real sanctions, that if anybody is guilty of all of this or any of it, what happens? Are there any sanctions of any sort that would sort of discourage someone from being involved in a negative kind of way?

I think, Dr. Ellis, let's start with you and then come around the room and let everybody comment on it.

Mr. ELLIS. Congressman Towns, the ultimate sanctions, I'm saying the extreme, under our Department human subject rules is denial to an institution of further research funds for human subject research.

Mr. TOWNS. I'm sorry, repeat it?

Mr. ELLIS. The ultimate sanction under our Department human subject protection rules is denial of the opportunity for further research funds from this point forward, let's say, to do human subject research.

Mr. TOWNS. Right, but if some of the things I'm hearing, you know, the point of that is if I'm hearing some of them might even have arrangements with the pharmaceutical companies, so all they need is one shot, and then after that, they can move on, so the point is that's my concern. For instance, all of a sudden you find out that there's conflict or corruption, whatever else, collusion, whatever you want to refer to it as, and then you say, well, from this point on, we're not going to deal with you, but the point is if a person has arrangements with a pharmaceutical company, then they're prepared to move on. So I think it has to be really thought out in a major kind of way where something happens that will further discourage people from being involved in that kind of way.

Anybody have further comments on that? I think this is a real issue here. We have all these IRBs out there, and of course nobody seems to know the number, what they're doing and how they're doing. Dr. Cassell.

Dr. CASSELL. I think the points you raise are important, but the future for IRBs will not be improved simply by being able to slap, no matter how hard, the wrist of a misperforming one as it will be improved by adequate staff and adequate training and adequate connection to a larger structure of IRBs in the country. They labor under, really, inadequate resources. They were set up for something much easier than where they are now, but there wouldn't be adequate resources by just saying, there wouldn't be adequate resources, unless there is a legislative intent behind it, at least legislative intent behind it that provides enough people to run an IRB and enough money to do it properly and enough education so the people who are sitting on that IRB knows something, are not just good hearted or kind, and they know enough not to take money, we all know that there are bad people everywhere, that's hard to argue, but there are less bad people where a structure is set up that encourages goodness than where a structure isn't even in place.

Mr. TOWNS. Any other comments on that? Yes.

Mr. YESSIAN. Congressman Towns, I have one point, and Laura McBride has one. On your point of structure, we talked about OPRR's location in the Office of the Secretary, well there's a very concrete issue there you could apply with academic health centers where there are IRBs, and I would say there you should assure there's adequate independence of the IRB. You don't have that, it seems to me, where you have an IRB that's part of a grants office as is sometimes the case, with the very office that's responsible for bringing in grants and contracts, typically from the pharmaceutical industry is the office that would oversee the IRB, in some cases representatives of that office are on the IRB itself, so I would say that's a conflict that we ought to watch out for.

Furthermore, investigators in these institutions are going to have industry money for their own projects. I don't think there's any getting around that or that there is anything wrong with that. But certainly, should recuse themselves for any project for any review that involves any project they're associated with, I think most probably do, but we should certainly make sure that happens.

Did you want to add something?

Ms. MCBRIDE. Along those same lines I'll reiterate a point we made before, the need for greater representation of independent members on the IRBs. As Dr. Lawrence said before, there could be 1 out of 20 or 50 IRB members, and independent voices can play a good role in balancing institutional voices, other members' conflicts, but also representing the interests and the perspectives of the community outside the institution.

Mr. YESSIAN. We've seen places where independent members have played that role and have raised questions that have made a difference.

Mr. TOWNS. Thank you very much. I yield, Mr. Chair.

Mr. MICA. Thank you, Mr. Towns. Dr. Ellis, in the hearing June 11, 1998, I think you testified, we have to date eight separate complaints about a body of research in New York City under the auspices of four institutions, and at that time you said you had not concluded your investigation. Have all of those investigations been complete?

Mr. ELLIS. Yes, all four are complete.

Mr. MICA. Could you provide us, for the record, with a summary of your resolution of those investigations?

Mr. ELLIS. Yes.

Mr. MICA. Dr. Ellis, you testified also at that hearing the last time your office suspended an assurance for human subjects research, I believe it was in 1991. From the hearing last June, what's the status of suspended human research subjects?

Mr. ELLIS. Mr. Chairman, I'll just have to go back to the hearing record to see exactly which institution I would have been referring to. I can't tell from your reading.

Mr. MICA. You said there was one suspension. Suspended an assurance for human subject research in 1991. Have there been any since the last?

Mr. ELLIS. Oh, I'm sorry, I misunderstood. Yes, OPRR suspended Rush Presbyterian St. Lukes Medical Center in October 1998. OPRR restricted the West Los Angeles VA Medical Center's assurance in March 1999, which caused the Department of Veterans Affairs to simultaneously suspend all research, human, animal and otherwise at its West Los Angeles VA facility.

Then in May 1999 OPRR suspended the assurance at Duke University Medical Center. I think that captures all the actions of the type you inquired on.

Mr. MICA. The IRBs that received Federal funds, is there in place a Federal registration requirement?

Mr. ELLIS. Yes, for any institution that receives research funds for human research from the Department of Health and Human Services, OPRR follows the money assiduously and receives a formal written agreement, we call it an assurance, from the institution. One component of that formal written assurance is the IRB roster or rosters, so I can say unequivocally for human subject research that falls within OPRR's purview, that we have the name and address of every IRB member.

Mr. MICA. But they're not required to register, it would be through that document, is that right?

Mr. ELLIS. That's right. For us it's a de facto registration.

Mr. MICA. And those who do not receive Federal funding are not required to register?

Mr. ELLIS. I shouldn't speak for FDA, but I understand that FDA has several data bases that include names and addresses of IRBs, but no comprehensive system of registration.

Mr. MICA. And the Inspector General had recommended that there be a registration, I believe, for all of these groups, is that correct?

Mr. ELLIS. That is a principal recommendation of the June 1998 report.

Mr. MICA. The other thing that concerns me is many of the recommendations that were presented by many of these groups could be instituted by at least for those who receive Federal funds to the IRBs, by an advisory memo from the Secretary or from the agency. Dr. Lawrence, do you think that might be possible?

Dr. LAWRENCE. OPRR communicates with its IRBs and through the granting systems frequently, and we can go back——

Mr. MICA. We're going to get a copy of all of those communications.

Dr. LAWRENCE. We can go back and take a look at the recommendations and see how we can educate our IRBs about what those recommendations are, and see if there are other actions that we need to take. I don't have a list of each and every, so——

Mr. MICA. Well, again, it seems like common sense. I come from the business sector, and it seems that some things can be done as advisory, and certainly these folks that are getting Federal money it can be made a condition of. I just can't understand why the Secretary or the agency cannot, at minimum, request some of these changes that have been recommended by the Inspector General, national medical college groups, American Psychiatric Association, by the President's Advisory Commission.

Dr. LAWRENCE. I understand your question, and I appreciate it as well. I'll restate that some of these things already have happened, especially with the issuance of the guidance. However, we can go back, sir, and we can go through——

Mr. MICA. I just throw that out as a suggestion. Then when we do the next hearings, which I'm sure Mr. Towns will be requesting——

Mr. TOWNS. Right.

Mr. MICA. You can't come in and say hey, we've done even this minute step in the right direction.

A final question here. Dr. Cassell, some of the things that you recommended, they require the expenditure of some funds. Should it be a requirement in the case of Federal funds going for research that those who receive that money contribute out of those funds sufficient resources to make certain that the recommendations you have are in place?

Dr. CASSELL. Yes.

Mr. MICA. Thank you. That's the best, most succinct answer we've had today.

Well, there are many additional questions that I would like to ask, and we will, with the permission of our ranking memoranda submit them to you for submission to the panel. I'll yield at this time for any final questions to Mr. Towns.

Mr. TOWNS. Thank you. I just have one final question. In this very vulnerable population that we're dealing with in some instances in research, the mentally ill and of course in some instances, I just sort of feel that maybe the structure should be different in research with that population. If the physician is involved in the research, it is my feeling that that physician is so involved that some of the other kinds of symptoms that they might not be watching them closely enough, so the structure should be in the case like that, that there should be a doctor that's not a part of the research really responsible for the medical well-being of his particular patient, because I think that they're very vulnerable, and you're so involved in research you just ignore everything else.

So I think that the structure should be different when you have a vulnerable population. I just need some quick comments on that. Yes, sir, Dr. Cassell.

Dr. CASSELL. That is a specific recommendation that NBAC made as part of its report. A specific and wise recommendation

that somebody besides the investigator have responsibility for the well-being of those patients.

Mr. TOWNS. Yes?

Dr. WALSH. I too think there's a lot of wisdom to that philosophy. IRB worried, when I was on it, and I hope still worries about it, because we still deal with a psychiatric population. So I think in many ways it's a solid recommendation that should be carried out. We in many instances have done it. We have, for example, a clinical team taking care of the patient and a research team who is not part of the clinical team.

The issue that is a tough call is where to draw the line, where does this level of vulnerability start. And frankly from trying to work our way through assorted research protocols, it never became a crystal clear line, where you could say I'm not comfortable, for example, saying all psychiatric patients must participate in the way that's just been described. Because many psychiatric patients are not particularly vulnerable, but some are very vulnerable, and where, how that gets decided I think is a very important question, which at the moment is wrestled with by IRBs.

Mr. TOWNS. Yes, Dr. Oldham.

Dr. OLDHAM. Mr. Towns, if I may add one point, I think that's a very important suggestion and a very important concern.

I would just want to add that I think there are many categories of vulnerable populations, and to focus on the mentally ill is one category and as Dr. Walsh said and I agree with this, some of these patients are particularly vulnerable, other of them may not be any different than the capable population.

There are others who are also potentially vulnerable who may not have mental illness, for example people with stroke, people with other kinds of incapacity and other with life-threatening terminal diseases which put them in a very vulnerable state, so I think all of these need to be looked at very carefully with the same level of concern.

Mr. TOWNS. I agree. Dr. Cassell.

Dr. CASSELL. There's no question what Dr. Oldham said is true, but that should not take away from the fact that the protection of persons with certain mental disorders require special attention if for no other reason than they have not received the attention up until this time whereas the other categories he mentioned are already, do already come under regulation and custom that is not present here.

Mr. TOWNS. Any other comments before we close out? Yes?

Mr. YESSIAN. I would just agree. Many have commented that the most vulnerable subjects are those that are already patients of the investigator. That's one of the reasons why I think it's especially important to look at informed consent, not just in the context of what's in that document, but how is it explained to a potential subject and who does it, and in certain kinds of trials, it may be especially important that that be a quite independent party that the potential subject can communicate with without getting in the way of the doctor patient relationship.

Mr. TOWNS. All right. Thank you very, very much. Thank you, Mr. Chairman. I yield back.

Mr. MICA. Just one question to Dr. Cassell. The Bioethic Commission that you're on, was formulated by Executive order, is that correct? It's still under Presidential Executive order?

Dr. CASSELL. That's correct.

Mr. MICA. What's your feeling toward codifying that?

Dr. CASSELL. I think that's important.

Mr. MICA. You would recommend it?

Dr. CASSELL. Yes.

Mr. MICA. Thank you.

We have additional questions which we will submit to the panel, and we are keeping the record open by unanimous consent for at least 3 weeks. At this time I'd like to thank each of our witnesses for being with us this morning into this afternoon, and for your cooperation. We have an important task before us. We need everyone's cooperation to make certain that we put in place proper safeguards and regulations and protections for people who participate in medical research and that's our intent, to see that that's done wisely, that we as Members of Congress see that the laws are changed and the administration of the laws and regulations is proper to protect the public and also public funds.

I thank you and I'll excuse the panelists at this time and call our second panel.

Our second panel today consists of Mr. Cliff Zucker, executive director of the Disability Advocates, Inc., of Albany, NY.

Our second witness is Dr. Adil Shamoo, and Dr. Shamoo is with Citizens for Responsible Care in Psychiatry and Research in New York City.

Our third panelist is Miss Charisse Johnson, and she is from Brooklyn, NY.

Our fourth panelist is Ms. Sherry Grenz, and she is with the National Alliance of Mentally Ill.

These four panelists make up our second panel. If they could all come forward, please.

As I explained to our first panelists and witnesses, this is an investigations and oversight subcommittee of the U.S. House of Representatives. We do swear in our witnesses. We also allow approximately 5 minutes to present your oral testimony before the subcommittee. Any additional records or lengthy statements will be made part of the record upon request. We're going to try to hold the panelists to those constraints today, particularly since the first panel ran us a little bit behind schedule.

I would like to welcome each and every one of you, and if you could please stand and be sworn.

[Witnesses sworn.]

Mr. MICA. The witnesses have answered in the affirmative.

I would like to welcome you this afternoon to our subcommittee hearing, and I will first recognize the statement, and we will go through all of the statements, then go to questioning.

I'll recognize Mr. Cliff Zucker, executive director of Disability Advocates of Albany, New York. Welcome, sir, and you're recognized.

STATEMENTS OF CLIFF ZUCKER, EXECUTIVE DIRECTOR, DISABILITY ADVOCATES, INC., ALBANY, NY; ADIL SHAMOO, CITIZENS FOR RESPONSIBLE CARE IN PSYCHIATRY AND RESEARCH, NEW YORK, NY; CHARISSE JOHNSON, BROOKLYN, NY; AND SHERRY GRENZ, NATIONAL ALLIANCE OF MENTALLY ILL

Mr. ZUCKER. Thank you, Chairman Mica.

I appreciate very much the opportunity to testify before the committee today. I am executive director of Disability Advocates, which is a not for profit public interest law office in Albany, NY and for the last almost 10 years we have attempted to advocate for the rights of human subjects of medical experiments who have medical disabilities.

The first thing I think that we have to remember is that if, to answer the question the committee poses, are Federal protections adequate, we need information, and that so long as IRB deliberations are cloaked in secrecy, that we can never really know what is going on there. A number of witnesses earlier made the point, but it really goes far beyond registration of IRBs and knowing how many IRBs there are. We also don't know what sort of experiments they approve, who the subjects are, what their characteristics are, whether they have mental disabilities, what the nature of the risks they are subjected to is, what the premises that are being studied are, and whether those are important premises.

It's been said that sunlight is the best disinfectant. I think we will go a long way toward protecting subjects if you enact legislation that would require the, both the registration of IRBs and annual reports of all experiments that are approved by IRBs and additional characteristics of human subjects and of the experiments which are detailed in my written testimony, which I request be made part of the record.

Mr. MICA. Without objection, so ordered.

Mr. ZUCKER. What I'm proposing is somewhat similar to a bill that Congressman Towns drafted and introduced I believe a year or two ago, which has a similar purpose.

The second thing that I'd like to call the committee's attention to is an experiment which was until very recently ongoing at Bellevue Hospital in New York City conducted there by New York University School of Medicine and funded by the Novartis Pharmaceutical Corp. The experiment was conducted using the experimental drug Iloperidone on homeless mentally ill individuals who were approached to be part of the research very shortly after admission to the hospital, within hours or days of being admitted to the hospital in a florid psychotic state.

One thing I want to highlight before I get into the details of that experiment is that my office filed a complaint with the Office of Protection for Research Risks concerning problems which I am going to outline. The Office of Protection from Research Risks declined jurisdiction, said that they did not have any jurisdiction to review the experiment of what the IRB had done here. These are major research institutions in New York City and they get a lot of Federal money and they conduct a lot of Federal research. They have an insurance, which is this contract with the Office of Protection from Research Risks, which in most instances requires them

to provide Federal protections to all of their research, even drug company funded research. However, NYU and Bellevue have exempted themselves from that and OPRR let them do it.

So we're in the remarkable situation where very serious complaints are raised about research of homeless, psychotic individuals that is allegedly conducted on their consent and OPRR says we can't touch it. That's a problem, I think it needs to be addressed by legislation.

Each of these subjects in this protocol arrived in the emergency room in a florid psychotic crisis. There were 14 subjects, we examined the records of all of them. Most of them are homeless. Within hours or days, they were approached to give informed consent to be patients in this experimental drug study and 14 of them did give that consent.

In every instance, the very same day or the day before or the day after, there are concurrent notes from clinicians describing these patients as floridly psychotic, as disordered thinking, as having no insight or judgment into their mental illness, as responding to voices, and yet in every instance sandwiched in between those comments about their florid psychosis, we have a note that says "we asked the patient to participate. We answered all his questions, we explained all the risks and benefits, and after that discussion he gave informed consent."

It's an interesting thing. There are 14 patients. The notes describing the informed consent process are word-for-word identical, hand written, word-for-word identical notes for every patient and they're not all entered by the same person, either. So it's a boilerplate purported description of an informed consent process, which is very apparent when you read these records that these patients were floridly psychotic and at this particular time they certainly were not capable of giving informed consent.

My written testimony contains, does not name the patient, uses a pseudonym, but it contains quotes from the record so you can judge for yourselves whether it's conceivable that these patients had a momentary, a moment of lucidity in which they could comprehend a multi page, complex informed consent document that I submit not too many college graduates could read and understand.

It's also significant that none of these subjects were tried on nonexperimental drugs and had failed on it before they were put into the experimental drug protocol. These were people who very likely would have responded well to conventional medications, including some of the more newly developed antipsychotic medications, but those are expensive, and there's a financial conflict of interest here for Bellevue Hospital, if they offered respiradol, that's an expensive drug they had to pay for, if they instead offered the experimental drug iloperidone they're paid to do it by the drug companies, so there's a conflict of interest there.

Every one of the patients did poorly on the study, they either withdrew themselves or were withdrawn by the experimenters, got much more psychotic. They were taken off the drugs, put on a placebo washout, then some of them were put on the drug, some put on placebo, they became so ill none of them could finish. When they were taken out of the program they were put on drugs, lo and be-

hold they got better, and discharged into the community or other facilities.

In my view it's unconscionable, when people are brought to the hospital in crisis, these are people dangerous to themselves or others, this is a life-threatening situation, some of them had dangerous histories of injuring themselves, threatening people, animals, that instead of given treatment, they're taken off treatment, given placebos and put on an experimental drug that wasn't proven to be effective and in every instance proven ineffective. The hospital has a desire to enroll patients, the institution has an impetus to enroll people and not pay for expensive drugs, who is looking out for the patient's interests? Supposedly it's the IRB. But it's interesting. The minutes of the IRB, the IRB considered this protocol on September 28th. On that day, the IRB considered 110 projects. The minutes, we were provided with the minutes of the September 28th IRB meeting. One page contains the minutes of five protocols. The minutes consist of at most three words per protocol, if you don't count the name of the protocol, the heading, if you count the substantive discussion of what happens, three words and the number voted for and against.

What it demonstrates is, without knowing more, I think we all know, you can't consider 110 protocols on 1 day. The kind of consideration that should have happened, that's required by the Federal regulations isn't happening.

Among other things, I think that you need to consider whether Federal law should limit the number of protocols that are considered by an IRB, should set actual limits for the workload, and should require that certain resources be devoted to this process, because right now these volunteer IRBs just can't possibly do the job. I might add again, echoing some of the things said earlier, that independent consent monitors would be very, very important, independent of the facility which has a lot to gain financially from enrolling subjects in these protocols.

Furthermore, I think we need to consider legislation that would make it unlawful to place acutely psychotic individuals who come to the hospital seeking care in experiments without first determining that they won't benefit from nonexperimental treatment, I think we have an ethical duty to first offer people what we know might work and to then only experiment if those things are unsatisfactory to them.

I want to also touch on the fenfluramine experiments.

Mr. MICA. Could you begin to conclude?

Mr. ZUCKER. OK, I'm going to refer you to my written testimony which contains very specific recommendations concerning changes in Federal law and statutory language that I think is worthy of your consideration. I think we need to make it clear that neither poverty, nor race, nor family relationship to a person who is accused of crime, nor being the parent, excuse me, being the child of parents who are allegedly poor parents is the kind of condition that permits children to be experimented on in a way that is impermissible with so-called normal, middle class children. What OPRR did in the fenfluramine case, if you look at what they did to Mt. Sinai, they condemned them for doing this challenge on middle class con-

trol children, but when they were poor children over here at Columbia University, it was OK.

It's just inconceivable to me that you can, that because you're poor, because you have older brothers in trouble, that such experiments can be conducted if they're impermissible to other children. You don't get special rights because you're poor. Thank you very much.

Mr. MICA. Thank you.

[The prepared statement of Mr. Zucker follows:]

December 6, 1999

The Honorable John L. Mica
Chairman
Subcommittee on Criminal Justice, Drug Policy and Human Resources
House of Representatives
Committee on Government Reform
2157 Rayburn House Office Building
Washington, DC 20515-6143

Dear Chairman Mica:

I am Executive Director of Disability Advocates, Inc., a not-for-profit public interest law firm which advocates for the rights and protection of persons with disabilities. For almost ten years, Disability Advocates has advocated for the rights and protection of human subjects of medical experiments, and in particular, the rights of children and mentally disabled human subjects. Children and persons with mental disabilities are least able to protect their rights and well-being as human subjects, and the current protections in federal law are inadequate to protect these vulnerable persons.

I. Secrecy of IRB Proceedings Makes it Impossible to Adequately Protect Human Subjects.

I appreciate the opportunity to testify at the public hearing on "Do Current Federal Regulations Adequately Protect People Who Participate in Medical Research?" A complete answer to this question will be elusive as long as the conduct of medical research remains cloaked in secrecy. The lynchpin of current protections for human subjects is the Institutional Review Board (IRB) which has the duty to review the conduct of human subject experiments to insure the protection of human subjects. The deliberations and actions of the IRBs occur behind closed doors in the institutions conducting the human subject research. There is no requirement that the IRBs report the nature and risks of the experiments approved and the characteristics of the subject population to any government oversight agency or to the public. As a result, we have little knowledge of what is occurring. Oversight by the Office of Protection from Research Risks (OPRR) is triggered by complaints or reports of adverse incidents, and thus only a tiny percentage of IRB decisions ever come to light or are reviewed. This must change if we are to develop a system to adequately protect human subjects. Federal law should require:

Collection of Data. All entities conducting human research shall yearly provide to the OPRR the following information related to all human research conducted by the entity in the past calendar year: (1) an abstract of each human research protocol which includes a description of the hypothesis being studied, the research procedures utilized, and the risks and benefits to human subjects presented by the procedures; (2) the number of subjects involved in each human research protocol; (3) a breakdown of the number of subjects involved in each human research protocol by race, ethnicity, age, sex, capacity to consent, and mental disorder that may affect decision-making capacity; (4) a statement as to whether the human research is considered by the Institutional Review Board to be non-therapeutic or potentially therapeutic; (5) a statement as to whether the human research is considered by the Institutional Review Board to present minimal risk or greater than minimal risk; and (6) the type of disease, illness, disability and/or symptoms studied in each human research protocol. All reported data shall be made available to the public upon request.

Had such reporting requirements been in place, many of the past abuses of human subjects would have been discovered early and remedied by public scrutiny and government oversight. At present, only a tiny percentage of human subject research ever sees the light of day.

II. Federal law must be strengthened, as demonstrated by psychiatric drug experiments conducted on the "consent" of floridly psychotic homeless mentally ill individuals.

Disability Advocates, Inc.has been investigating research which was conducted at Bellevue Hospital in New York City, conducted by New York University School of Medicine, and funded by Novartis Pharmaceuticals Corporation. The protocol, ILP3000, tests the experimental drug Iloperidone on patients with acute or subacute exacerbation of schizophrenia. We have examined the records of the fourteen patients who were enrolled in the protocol.

Each of the subjects arrived at the emergency room in a florid psychotic crisis. Most were homeless. Within hours or days, each floridly psychotic subject was asked to enter the Iloperidone study. There is no indication that any of these subjects had been tried and failed on available non-experimental treatments before being offered experimental treatment.

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Every subject's case record contains an identical "boilerplate" entry purporting to describe the informed consent process, asserting that all the subject's questions were answered and that "all risks and benefits of participating in this study have been discussed with the patient who understands that participation is voluntary and that they may withdraw consent at any time." Every record has

concurrent notes from clinicians noting that the patient is acutely psychotic and lacking in insight and judgment. In no case is there any attempt to reconcile the concurrent notes describing acutely disordered thinking with the "boilerplate" notes describing an informed consent process which is made to sound calm and contemplative. While the informed consent forms contain a capacity certification by a Bellevue psychiatrist, there is no note or report describing the capacity assessment or explaining why the subject had capacity notwithstanding his or her florid psychosis.

In every case, the subject either withdrew because he or she could not tolerate participation, or was terminated by the researchers because the subject was doing so poorly. In no case did the subject derive any benefit. Each subject, to varying degrees, suffered exacerbation of psychotic symptoms due to delay in receiving medication while on the placebo/washout phase or when receiving the drug. On withdrawal from the experiment, all patients were treated with non-experimental drugs that could have been offered upon admission, and many of the subjects shortly improved enough to be discharged. None of the records contains a justification for withholding treatment that was likely to be helpful to these acutely sick individuals.[1]

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[1]The record of one patient is illustrative. Mr. Doe (a pseudonym) was admitted to Bellevue Hospital in New York City on December 31, 1998. He was eighteen years old and was "acutely psychotic," "floridly psychotic" and "unable to care for self at this time" according the Emergency Admission form. On January 4, 1999, "Pt. denied need for meds or group therapy during AT [activity therapy] orientation." On January 5, 1999, the caseworker states that he "is in complete denial with his illness." A note that day describes him as ""agitated and uncooperative" and states "[h]e has no insight into his illness and exhibits poor judgment...." Notably, a social worker had a lengthy telephone conversation with Mr. Doe's mother on January 5, 1999, but there is no indication in the record that his mother was advised that he was to be asked to participate in an experiment. Later that day, the record states "patient approached staff claiming he was hearing voices."

Doe had responded favorably in the past to Risperidone, a non-experimental anti-psychotic, but he was not offered Risperidone. Instead, on January 6, 1999 he was asked to participate in the Iloperidone study.

Doe's participation was risky for himself and others. The medical records state that since childhood he had heard voices which commanded him to hang and burn a dog, kill a cat by throwing it out the window, attempt suicide, and threaten to poison his siblings. The experiment involved a placebo washout period in which he would receive no medication, followed by either a placebo, Iloperidone, or another medication. Therefore, the experiment offered the possibility of no treatment for an extended period, notwithstanding this dangerous history.

Given the extraordinary risks of harm to self or others from withholding effective treatment from acutely psychotic patients, it was clearly in the patients' best interest to receive prompt non-experimental treatment before being offered an unproven experimental drug or placebo. Had the patients' welfare been the primary consideration, they would not have been asked to participate unless they had been tried and failed on non-experimental treatments. In discussions with NYU IRB members and the principal investigator, it was revealed that because of concerns about cost, some of the newer, more effective antipsychotic medications, such as Risperidone, are not routinely offered to patients at Bellevue Hospital. This information was offered to justify offering an experiment rather than treatment to acutely psychotic patients.

III. It is time to enact special protections for persons who may be incapable of giving informed consent due to mental disability.

The Iloperidone study demonstrates the need for legislation to ensure that acutely psychotic individuals seeking care for a psychiatric emergency are offered treatment, and are not solicited for experiments before non-experimental treatments have been tried and failed. These individuals are in no position to understand that it is a "therapeutic delusion" to assume that doctors would not ask them to participate in an experiment that is not in their interest. Because the hospital can save money on expensive drugs, and the researchers desire to enroll subjects, no one is putting the patient's needs first.

In the course of our investigation we requested copies of the IRB minutes regarding the protocol. On September 28, 1998 the NYU IRB considered 110 projects according to the agenda dated September 23, 1998. The number of matters considered on that date raises questions about the adequacy of the review, particularly in light of the uninformative minutes of the meeting. The minutes for five of the protocols reviewed that date consist of at most three words concerning each protocol. This is not an isolated incident. Other investigators have reported similar problems at a variety of research institutions. Federal law should limit the number of protocols which can be considered on one date by an IRB, and require the reporting of such statistics to OPRR, with the data to be made available to the public.

The federal "common rule" regulations governing human subject research contain no special protections for persons who may be incapable of giving informed consent due to mental disability, although such protections were proposed by the 1979 Belmont Report that led to the enactment of the common rule. More recently, the National Bioethics Advisory Commission has proposed special protections for these vulnerable subjects, but DHSS has not proposed or enacted such regulations. It is time for Congress to act, since the administrative agencies have not. I propose legislation to codify the following special protections:

Impermissible human research.

(1) No greater than minimal risk, non-therapeutic human research

shall be conducted on children.

(2) No greater than minimal risk, non-therapeutic human research shall be conducted on adults who are incapable of giving informed consent to the human research. Provided however, that it is permissible to conduct research on an adult subject who is incapable of giving informed consent to human research if (a) when previously capable, he or she gave advance consent to participation in the human research; (b) a relative or close friend of the subject is authorized to monitor the progress of the human research and has the authority to withdraw the subject if continued participation is not in the subject's interest; and (c) the relative or close friend has access to the advice of a physician independent of the human research to assist in such monitoring.

(3) No potentially therapeutic greater than minimal risk human research shall be conducted on an incapable subject without the consent of the guardian of the subject who is authorized to consent to experimental medical treatment or without authorization by a court after a finding that the subject is incapable and that the subject's participation in the human research is in the subject's best interests, considering: (a) the risks and potential benefits of the human research; (b) the available alternatives, including not treating the condition; and (c) whether the human research is consistent with what is known of the subject's wishes, beliefs, values and desires, or unless when previously capable, the subject gave advance consent to participation in the human research

(4) Regardless of capacity, no adult person shall be a subject of human research if he or she objects to participation in human research.

(5) Regardless of capacity, no person shall be a subject of human research without notice that he or she is to be a subject of human research and notice of the right to object to such participation.

IV. The Fenfluramine experiments on healthy young minority children demonstrate the inadequacy of current protections for racial minorities. the poor, and children.

Disability Advocates filed complaints against New York State Psychiatric Institute (PI), Mt. Sinai School of Medicine (Mt. Sinai) and Queens College in December, 1997 and February, 1998. The complaints involved non-therapeutic experiments on young child subjects using the drug fenfluramine.

The experiment at PI involved thirty-four healthy boys, between the ages of six and ten, who were younger brothers of convicted delinquents. They underwent a "challenge" experiment with the

drug fenfluramine. The study was wholly non-therapeutic, and designed to test a hypothesis about the effect on a child's brain chemistry of living in an environment with poor parenting and other stressors. The boys "were all from impoverished families; 44% were African-American and 56% were Hispanic." The boys had never been in trouble with the law, and had no disorder or condition other than the social situation described above. The boys fasted for twelve hours prior to the test, and during the test had access to water only. An intravenous catheter remained in place for five and one half hours. During that period, a single oral dose of fenfluramine hydroxide was administered and blood was drawn hourly.

The experiments conducted by Mt. Sinai and Queens College involved boys, aged seven to eleven years of age, who underwent a "challenge" with the drug fenfluramine. The experiments were wholly non-therapeutic, and designed to test an hypothesis about how the brain chemistry of children with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) is related to aggressive behavior. In both experiments, the boys who were taking medicine were subjected to a one month "washout" period during which they were removed from all medication. The boys fasted overnight prior to the test, and during the test. An intravenous catheter remained in place for seven hours. During that period, a single oral dose of fenfluramine was administered and blood was drawn hourly. The experiment also involved "normal controls."

In June 1998, OPRR issued its findings concerning the complaints. OPRR sharply criticized Mt. Sinai and Queens College for procedural and substantive deficiencies in the research. OPRR found that it was impermissible to conduct the research on "normal control children" because they did not have the condition being studied and therefore could not legally be subjected to greater than minimal risk experiments.

By contrast, PI was inexplicably exonerated. This OPRR conclusion is inconsistent with the findings regarding Mt. Sinai and Queens College, and contrary to federal regulations. The OPRR action was apparently based on the conclusion that being poor and having a brother who is a juvenile delinquent is a "condition" that makes it permissible to conduct otherwise impermissible experiments on children.

OPRR found that the fenfluramine challenge exceeded the limits of minimal risk as defined by HHS regulations at 45 CFR 46.102(i), and therefore concluded that the research did not meet the requirements of HHS regulations governing research involving children at 45 CFR 46.404, 46.405, or 46.406 as regards the "normal control children" in the Mt.Sinai/Queens College research. This is because under the regulations, greater than minimal risk research on children can generally only be approved when the procedure is likely to yield generalizable knowledge about the subjects' condition which is of vital importance for the understanding or amelioration of the subjects' condition and the procedure presents experiences to subjects that are reasonably commensurate with those inherent in actual or expected medical, dental, social or educational condition. Therefore, OPRR correctly faulted Mt. Sinai and Queens College for including four "normal" children as controls because these

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The Honorable John L. Mica
December 6, 1999

children did not have the condition, attention deficit hyperactivity disorder (ADHD), being studied.

OPRR found the research at PI to be unobjectionable because the IRB found that "the procedure was likely to yield generalizable knowledge about the subjects' condition which is of vital importance for the understanding or amelioration of the subjects' condition" and that "the procedure presented experiences to subjects that were reasonably commensurate with those inherent in actual or expected medical, dental, social or educational condition." But OPRR did not explain what factual basis there is for these IRB findings, and there is none.

No doubt the healthy young subjects of the PI research had not previously experienced placement of an indwelling intravenous catheter for serial blood drawing, administration of fluids, and a fenfluramine challenge. Because these young boys had not previously had such experiences, and were not likely to encounter them outside the research, the research was not permissible under 45 CFR 46.406(b). Certainly, these procedures were as alien to the subjects at PI as they were to the "normal control" subjects at Mt. Sinai.

Although the subjects were poor young children whose older brothers were adjudicated juvenile delinquents, OPRR failed to explain how this is a "condition" within the meaning of the HHS regulations. The children had never been diagnosed with a medical or psychiatric condition prior to entry into the research. And even if some of the children left the research project with such a diagnosis, others did not and thus never were diagnosed with any condition. Had PI included middle class children who were unrelated to juvenile delinquents in this research as controls, presumably OPRR would have faulted PI, as it faulted Mt. Sinai. Can it be that federal law allows poor children to be subjected to non-therapeutic experiments that are prohibited on middle-class children? Poor children are no less deserving of protection than are middle-class children, and poverty is not a "condition" that confers lesser rights at law.

In cities like New York, where the poor are disproportionately minority, OPRR's decision has a discriminatory impact on minority children who will be subject to experiments that may not be conducted on middle-class children. This is demonstrated by the exclusively minority racial composition of the PI subjects. By authorizing such discrimination, OPRR violates rights protected by Due Process and Equal Protection.

Surely the sins of their brothers cannot in any way reduce the protections due innocent children who are subjects in the PI experiments. It is ironic that federal regulations contain explicit protections for prisoners, and that the juvenile delinquent older brothers who are incarcerated are protected by these regulations. See 45 CFR 46.301 et. seq. The fenfluramine challenge would have been prohibited on prisoners because it involved more than minimal risk, more than inconvenience to the subjects, and has not been approved by the Secretary of HHS. See 45 CFR 46.306(a)(2). Although the fenfluramine challenge is impermissible with prisoners, such as the juvenile delinquent brothers of the PI subjects, and is impermissible with middle class controls, OPRR claims it is

permissible with innocent six to eleven-year-old children who have the misfortune to be poor and have an older brother in trouble with the law. Federal law should not permit such an absurd result.

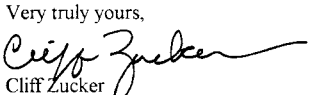
Federal law should make it clear that neither (a) poverty, (b) race, (c) familial relationship to a person who has been accused or convicted of a crime, nor (d) being the child of parents alleged to have poor parenting skills is a "condition" which would permit the conduct of human subject research which would be impermissible on so-called "normal" children. I urge you to enact legislation.

In the PI research, all the subjects were either African-American or Latino. This violated 45 CFR 46.111(a)(3) which requires "equitable" selection of subjects, particularly when the subjects are "vulnerable" populations or "economically or educationally disadvantaged persons." Even if the exclusion of all Caucasians was not by design as claimed, such an imbalance should have been noted and corrected. I propose amending federal law to provide:

> **Exclusion or inclusion of subjects in human research based on race or ethnicity.** When race or ethnicity is proposed to be a factor affecting either inclusion or exclusion from human research: (1) inclusion and exclusion criteria, and the rationale for such criteria, must be reported by the entity conducting the human research to the Secretary of HHS; and (2) the human research may not be conducted without the approval of the Secretary. Such request for approval and the decision of the Secretary shall be a public record. This provision does not apply to attempts to enroll subjects based on race or ethnicity, when such enrollment is an attempt to replicate in the research the representation of these races and ethnicities in the population of the United States.

Thank you for the opportunity to testify on this important issue.

Very truly yours,



Cliff Zucker
Executive Director

Response to Committee

1. Should the Department of Health and Human Services develop guidelines and criteria to determine the effectiveness of IRBs? If so, what kinds of considerations should these guidelines take into account?

Yes, HHS should develop guidelines and criteria to determine the effectiveness of IRBs. In our report, we recommended that IRBs should be subject to periodic evaluations focused on determining their effectiveness. The Presidential Advisory Committee on Human Radiation Experiments and a panel of the Institute of Medicine made similar recommendations in their work.[1] Currently, HHS bodies with oversight responsibilities for human-subject protections conduct no such regular evaluations. OPRR's evaluations, which are the most thorough and hard-hitting, are most often in response to a complaint or incident. FDA is on site more often, but their reviews are generally narrow, procedural reviews.

Performance-focused evaluations would allow IRBs to continue to develop innovative practices in protecting human subjects while holding them accountable for results. The guidelines for what determines an effective IRB should be developed by Federal bodies in concert with those knowledgeable in the field, including IRB representatives, investigators, ethicists, and subject representatives. It is particularly important that the guidelines address the adequacy of the informed consent *process*. Too often now the emphasis is on the content of the informed consent document and on assurances that they have been signed by the human subjects. We need greater attention devoted to how the process is working and on how well potential subjects understand the consent documents they sign.

2. In the current system, we rely on researchers to report adverse reactions or side effects involving human beings in research trials.

- **Should we require that research participants complete an exit interview that includes reporting of adverse reactions and other information about the way in which the study was conducted?**
- **Should these reports by participants be made a part of the record of the experiment?**

I would suggest caution on any new requirements that have the potential of adding

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[1] Advisory Committee on Human Radiation Experiments, *Final Report*, (Washington, DC: U.S. Government Printing Office, 1995), Chapter 18, Recommendation 13(1).

RE Bulger, EM Bobby, and HV Fineberg, Editors, *Society's Choices: Social and Ethical Decision Making in Biomedicine*, (National Academy Press: Washington, DC, 1995), p. 182.

unnecessary time and complexity to the research process. However, it certainly seems reasonable to give participants *an opportunity* to complete an exit interview to address their experience in the research process and to make the results of that interview part of the record. This could help reinforce for the research team the importance of human subject protections and could be helpful to IRBs and others conducting continuing reviews of research.

3. In your testimony, you propose the private accreditation of IRBs.

- **Would this be like the accreditation that is currently used with hospitals?**
- **Who should take the lead in establishing this kind of accreditation?**
- **What would the federal role be in accreditation?**

In my testimony, I did not seek to propose accreditation of IRBs. Rather, I attempted to reference a potentially important initiative in the private sector. I see the accreditation of IRBs as a potentially effective way of raising the bar for IRB performance. As in other sectors, it could serve as an ongoing mechanism for developing state-of-the-art standards for the field and for applying them in ways that facilitate continuing improvement. The leadership for this effort, I believe, is properly centered in the private sector.

With respect to hospitals, Congress has stipulated that hospitals accredited by the Joint Commission on Accreditation of Healthcare Organizations are *deemed* to be in compliance with Medicare Conditions of Participation. It is premature to consider any such deeming authority with respect to IRBs.

The Federal role, I believe, should focus on providing leadership and oversight that fosters adherence to the human-subject protections specified in Federal law, independent of the accreditation movement. This would not preclude Federal efforts to facilitate the accreditation of IRBs, nor would it preclude some future efforts to develop ways in which Federal oversight and private accreditation efforts might be linked. In that regard, the accreditation experiences of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) could serve as a helpful reference point.

Mark R. Yessian
Regional Inspector General
U.S. Department of Health and Human Services

Mr. MICA. I'll now recognize Dr. Shamoo who is with the Citizens for Responsible Care in Psychiatry and Research. Dr. Shamoo, you are welcome and recognized, sir.

Mr. SHAMOO. Thank you, sir. I'm Adil Shamoo from Columbia, MD. I am here to speak today on behalf of thousands of families who are not able or willing to speak for themselves. I'm here to speak on behalf of Citizens for Responsible Care in Research. Just for identification, I am a professor at the University of Maryland School of Medicine, former chairman, I have been addressing questions on issues of research, have written extensively for several years, I'm editor in chief of a journal called Accountability in Research where I study and the papers submitted to our journal study the issues of integrity in research and how it is conducted ethically.

I also have chaired seven international conferences on issues of ethics on research.

I would like to thank you, Mr. Chairman. I also would like to ask that my entire statement be entered into record.

Mr. MICA. Without objection, so ordered.

Mr. SHAMOO. I will give simply highlights of my testimony, since the first panel covered a lot of ground.

I would like to thank you, Mr. Chairman, and members of the subcommittee to give me this opportunity to inform you of my personal and organization's grave concerns regarding current ongoing and ethical research practices. Vulnerable human beings, such as children, veterans, and mentally disabled individuals are being used as human subjects in high risk experiments with no potential medical benefit which cause them harm. It was our organization that brought the public attention to the fact that fenfluramine was given experimentally to minority children.

The voluntary, comprehending, informed consent is universally recognized as a fundamental human right. It must be applied to all human beings, be they privileged or disadvantaged. Our national public policy was formulated to provide safeguards aimed at preventing unethical human experimentation, such as the notorious New York Willowbrook hepatitis experiments conducted on mentally retarded children in the 1950's and 1960's and the Tuskegee syphilis study conducted on African American men in the 1940's to 1970's. But current Federal safeguards are inadequate, especially for mentally disabled persons and disadvantaged children. These groups are incapable of protecting themselves from unwanted, coercive even harmful experimentation.

It is the government's obligation to strengthen protection because the current regulation have proved to be inadequate, leaving researchers to circumvent them.

The rights of the powerless and disadvantaged individuals must not be compromised for the benefit of the powerful and the politically influential biomedical research establishment. To claim that individual rights must be sacrificed for the good of society is a self-serving motive which is not an ethical justification for overriding the rights of some incapacitated individuals. The universally adopted Declaration of Helsinki unequivocally affirms that, "the interest of science and society must never take precedent over consideration related to the well-being of the subject."

The violations and experimental procedures that greatly concern us are, and one is the abrupt washout experiment which you heard of and I will not give you more detail.

Second is the chemical challenge, the studies conducted on various human beings and third, the wholesale violations of informed consent.

The principle of informed consent is intrinsic to a democracy and can rarely if ever be violated. Perhaps in the event of national emergency, or for compelling public safety reasons. There are no compelling reasons to justifying experimenting on disabled human beings without gaining their informed consent. Involuntary research on disabled and the disenfranchised individuals does not serve the good of society. To the contrary, such research threatens its fundamental moral underpinnings.

Drug washout and chemical challenge experiments designed to produce rather than prevent a psychotic relapse in order to study its effect and conduct-photo imaging brain scans. They have routinely been approved by IRBs, thereby demonstrating that IRBs do not protect the interests of a subject and let me digress. Those fenfluramine experiments were approved by four different IRBs, four different grant proposals to four different study sections within the NIH and they were funded and carried over by four different sites within our research institutions.

I will give you some of our recommendations. These are concrete recommendations.

One; a moratorium on abrupt drug washouts and chemical provocation experiments that are likely to exacerbate severe incapacitating illnesses and expose vulnerable persons to addictive drugs, which may with repeated exposure lead to addiction or cause toxic brain damage.

The enactment of National Human Subject Welfare Act to cover all human subjects enrolled in research, whether supported by Federal or private sources of funding. This act, and I want everybody to pay attention to this, this act brings protections to human beings at least to a comparable level to the protections available since 1966 for animals through the National Animal Welfare Act. That means if we just take the National Animal Welfare Act and substitute "human beings," human beings will have greater protection because in this country you cannot conduct an experiment on animals, regardless of the source of funding, regardless of the site of research conducted without going through, applying the requirement of the Federal regulations. That is not, ladies and gentlemen, the case with human beings.

There is a lot of research, tens of thousands of patients in research experiments are not regulated, and he just gave you one of thousands of examples.

Three; a prohibition of conducting above minimal risk experiments on those incapable of evaluating the risks or appreciating the consequence to themselves unless they can be demonstrated to be in their interests. Mental capacity should be assessed by an independent physician and informed consent procedures should be monitored by independent observers. I'm very pleased to see NBAC and Dr. Oldham himself say that's an appropriate way of evaluating that. When I stated that in 1993, that was considered a heresy.

Four; establish an independent, community based, that's important, review board to provide oversight for research involving vulnerable human beings. Protected classes must be represented whenever such individuals are being considered as subjects, and investigators must be held accountable for the conduct of the research and the well-being of human subjects.

Let me tell you something about IRBs. IRBs are employees of the research institution. They get their paycheck monthly from that research institution which is trying to get millions of dollars from the pharmaceutical company and Federal Government. There is an inherent conflict of interest in that design.

Five, require no fault liability insurance for every human subject of research to cover, this should satisfy Congressman Mica this is not a Federal bureaucracy, require the human subject research to cover, that is no fault liability insurance to cover the duration of the research and 1 year following completion of the research. We believe such insurance, in the amount of about $250,000 per subject, would be an incentive to reduce unnecessary risks and would compensate individual families for undue harm. It would also reduce the taxpayers' burden for uninsured persons who may require costly aftercare as a result of experimental adverse consequences.

In closing, Mr. Chairman, the current state of protection for the vulnerable among us is very poor and it requires Federal regulations to strengthen, close the loopholes and mandate accountability for the harm done to our citizens and I thank you, Mr. Chairman.

Mr. MICA. Thank you.

[The prepared statement of Dr. Shamoo follows:]

The Need For Better Protections For Vulnerable Groups When Used In Research Experimentation*

Testimony
To

Subcommittee on Criminal Justice, Drug Policy, and Human Resources
Committee on Government Reform
U.S. House of Representative
United States Government

by

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December 9, 1999

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[1]The professional affiliation is given only for identification. I do not speak for the institution. I do speak for the organization, Citizens for Responsible Care in Psychiatry and Research.

Dear Mr. Chairman:

I am Adil E. Shamoo from Columbia, Maryland (see Appendix for brief biography). I am here today to speak on behalf of thousands of vulnerable patients and their families not able or not willing to speak for themselves. I am here to speak on behalf of Citizens for Responsible Care and Research.

I would like to thank you Mr. Chairman and members of your Subcommittee for giving me this opportunity to inform you of my personal and my organization's grave concerns regarding **current ongoing** unethical research practices. Vulnerable human beings such as children, veterans, mentally disabled individual are being used as human subjects in high risk experiments with no potential medical benefit which cause them harm.

It was our organization that brought to public attention the fact that Fenfluramine was given experimentally to minority children in NYC. . This drug was already known to cause harm since 1980's'. In the past year, the federal Office of Protection from Research Risk (OPRR) has temporarily halted research in a half a dozen major institutions nationwide.[1,2] Just in the past few weeks, major newspapers headlines indicate that thousands of research subjects are at risk from profit seeking researchers and industry. The New York Times, November 30, 1999 headline: **"When Physicians Double as Enterpreneurs**.[3] The Washington Post November 21, 1999 headline: "**Hasty Decisions in the Race to a Cure?—Gene Therapy Study Proceeded Despite Safety, Ethics Concerns**."[4] NY Newsday November 23, 1999 headline: **"Ethics" The Human Factor.**"[5]

These evidence behind these headlines should prompt congress to strengthen protection of vulnerable groups in research.

The voluntary, comprehending, informed consent—is universally recognized as a fundamental human right. It must be applied to all human beings, be they privileged or disadvantaged. Our national public policy was formulated to provide safeguards aimed at preventing unethical human experimentation such as the notorious New York Willowbrook hepatitis experiments conducted on mentally retarded children in the 1950's-1960's and the Tuskegee syphilis study conducted on African-American men in 1940's-1972.[6] But current federal safeguards are inadequate—especially for mentally disabled persons and disadvantaged children. These groups are incapable of protecting themselves from unwanted coercive, even harmful experimentation. It is the government's obligation to strengthen protection because the current regulations have proved to be inadequate leaving researchers to circumvent them.

The rights of powerless and disadvantaged individuals must not be compromised for the benefit of the powerful and politically influential biomedical research establishment. To claim that individual rights must be sacrificed *for "the good of society"* is a self-serving motive which is not an ethical justification for overriding the rights of some incapacitated individuals. The universally adopted Declaration of Helsinki unequivocally affirms that: *"The interest of science and society must never take precedence over considerations related to the well-being of the subject."* The violations and experimental procedures that greatly concerns us are:

1. **Abrupt drug "washout" produces**. These contradict the American Psychiatric Association clinical practice guidelines for schizophrenia patients.[8] Yet, thousands of such vulnerable patients are put at serious risk of harm in experiments that include abrupt drug "washouts".

2. **Chemical "challenge studies."** These are experiments in which incapacitated patients are injected with dangerous, neurotoxic drugs—including drugs of abuse, such as: amphetamine, methylphenidate, ketamine, cocaine, L-dopa, MCPP, fenfluramine, among others.

3. **Wholesale Violations of Informed Consent**. The principle of informed consent is intrinsic to a democracy and can rarely if ever be violated—perhaps, in the event of a national emergency or for compelling public safety reasons. There are no compelling reasons to justify experimenting on disabled human beings without gaining their informed consent. Involuntary research on disabled and disenfranchised individuals does not serve the *"good of society"*—to the contrary, such research threatens its fundamental moral underpinnings.

"Drug washout" and "chemical challenge" experiments are designed to produce—rather than prevent—a psychotic relapse in order to study its effects and conduct photo-imaging brain scans. They have been routinely approved by IRBs, thereby demonstrating that IRBs do not protect the interest of the subject.

The human consequences of "drug washout" and "chemical challenge" studies include relapse and death from suicide, cardiac irregularities, and "fatal accidents."[9]

Severely debilitating experiments such as these are not permissible in any other field of biomedical inquiry. They are morally reprehensible and medically unsupportable.

Yet, doctors who are sworn to "do no harm" are undermining the welfare of disadvantaged patients for purely speculative and conjectural purposes that have absolutely no therapeutic potential for those patients. For example, the Boston Globe's[9] investigative four-part series, "Doing Harm: Research on the Mentally Ill," (November 15-18, 1998) demonstrated how thousands of mentally disabled patients suffer relapses in high-risk, non-therapeutic experiments. The Globe reported the number of deaths that resulted from recent clinical trials on anti-psychotic drugs that required drug "washout"[9] in schizophrenia patients. The body count was:

In Zyprexa/olanzapine clinical trials was 27-of which 15 were suicides;

In Risperdal/risperidone there were 20 deaths-of which 4 were suicides;
In Seroquel/quetiapine clinical trials there were 14 deaths-of which 4 were suicides;
In Certindole clinical trials the rate of death was 27-of which 7 were suicides.

Based on their investigations, the Globe reporters found that even in potentially therapeutic experimental drug trials for schizophrenia, one in every 138 subjects dies and in some studies, 80% drop out ("lost with no follow-up). In N Y C, at Bellevue Hospital's Emergency Room, mentally ill homeless persons--who are in a psychotic state--are being recruited by doctors for commercially sponsored drug trials. These individuals are clearly incapable of giving informed, comprehending consent.[12]

Citizens for Responsible Care and Research has been singularly instrumental in exposing the nature and human consequences of these acute psychosis-inducing experiments conducted on mentally disabled persons.[10] These revelations have led the Director of the National Institute of Mental Health (NIMH) to evaluate current clinical studies conducted by NIMH. His examination resulted in an unprecedented action: -- 30 out of 108 clinical experiments at NIMH's own clinical research centers were suspended because they failed to meet ethical standards. Of the remaining 71 studies, more than 50 failed to justify scientific objectives.[2]

Because of the object of clinical research is not to provide the best therapeutic treatment to each individual patient-subject, but rather to gather scientific information, the individual patient's best interests may not be well served. Therefore, it is a moral imperative that only voluntary human subjects—who can comprehend and appreciate the risks, involved and are capable of making rational choices—be included. But mental patients and children are serious disadvantaged; they lack health care insurance; they lack the protection of responsible physicians who can advocate for their interests; and they lack legal safeguard to prevent them from being exploited. These vulnerable citizens are

left to the mercy of government-funded researchers who often put their financial interests above the welfare of these human subjects.

We are concerned that the recommendations circulated by New York's DOH are but another version of the State's previous regulations which were ruled unconstitutional.[7] Those recommendations are an attempt to legitimize involuntary, non-consensual human experimentation on disadvantaged, mentally disabled persons—a so called *"protected class."* Such a policy would, in essence, strip the most vulnerable citizens of their fundamental human right. These DOH-sponsored recommendations would permit non-consensual research to be conducted on *"decisionally incapacitated individuals"*—even if the research *"presents...risk to the research subject" causing "clinically significant deterioration,"* [D-9] and offers no *"reasonable prospect of direct benefit to the research subject."* [D-56] Both of the State's versions would permit non-therapeutic experimentation involving unacceptable risks to be conducted on individuals who lack the capacity to give informed consent. Both versions are an attack on individual human rights.]

A powerful confluence of self-interest groups, led by the pharmaceutical industry and their beneficiaries, are lobbying to promote their financial interests. Clinical research is a lucrative business—especially in psychopharmacology. Drug companies pay up to $35,000 for every schizophrenia or Alzheimer patient recruited into each drug trial.[11] Those lobbying for approval to conduct medical experiments on non-consenting persons of the vulnerable include, The American Psychiatric Association, the psychiatric research establishment and the all powerful pharmaceutical industry. Also lobbying against human rights are private and county hospitals who profit from industry-sponsored drug trials; and the lawyers who represent these special-interest groups.

Who lobbies on behalf of the voiceless and disabled? Who advocates for the rights and welfare of disadvantaged families that lack social and financial resources are not connected politically, and whose relatives are targeted for non-therapeutic,

debilitating experiments? Who advocates for disabled persons whose families have abandoned them?

Citizens for Responsible Care & Research Oppose All Unethical Research
We call for:

1. A moratorium on abrupt drug "washouts" and "chemical provocation" experiments that are likely to exacerbate severe, incapacitating illnesses, and expose vulnerable persons to addictive drugs which may, with repeated exposure, lead to addiction and/or cause neurotoxic brain damage.[12,13]

2. The enactment of National Human Subject Welfare Act to cover all human subjects enrolled in research whether supported by federal or private sources of funding. This act will brings protections to human beings at least to a comparable level to the protection available since 1966 for animals through the National Animal Welfare Act.

3. A prohibition on conducting above minimal risk experiments on those incapable of evaluating the risks or appreciating the consequences to themselves—unless they can be demonstrated to be in their best interest. Mental capacity should be assessed by an independent physician, and Informed Consent procedures should be monitored by independent observers.

4. Establish an independent, community-based review board to provide oversight for research involving vulnerable human subjects. Protected classes must be represented whenever such individuals are being considered as subjects, and investigators must be held accountable for the conduct of the research and the well-being of the human subjects.

5. Require no-fault liability insurance for every human subject of research to cover the duration of the research and one-year following completion. We believe such insurance, in the amount of about $250,000 per subject (premiums to be paid by the sponsor/research team/institutions) would be an incentive to reduce unnecessary risks and would compensate individuals/family for undue harm. It would also reduce the taxpayers' burden for uninsured persons who may require costly after-care as a result of experimental adverse consequences.

In closing, Mr. Chairman, the current state of protection for the vulnerable among us is very poor and it requires federal regulations to strengthen, close the loop holes, and mandate accountability for the harm done to our citizens.

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1. Office of Protection from Research Risk (OPRR) (1999). "Letter of March 22, 1999, from OPRR to VA Greater Los Angeles Healthcare System.

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APPENDIX

12/09/99

BIOGRAPHY OF ADIL E. SHAMOO, Ph.D.

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Born: August 1, 1941

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A research scientist with over 30 years experience in the laboratory with over 200 papers in the field of biophysics, biochemistry and ethics, science and public policy. Currently, a professor and former chairman of Department of Biochemistry and Molecular Biology and a member of the graduate faculty of Applied Professional Ethics, and affiliated with the Center for Biomedical Ethics at the University of Maryland, Baltimore. Dr. Shamoo consults on Ethics and Science. He chaired seven international conferences on ethics in research and public policy. The last two conferences he chaired in 1995 and 1998 were on Research and Decisional Capacity. Dr. Shamoo has testified on this issue before Congressional Committees and the National Bioethics Advisory Commission. Dr. Shamoo served from 1995-1998, on the Maryland Attorney General's Task force to propose legislation to protect the decisionally impaired human subjects in research. In this regard, Dr. Shamoo when serving on the Board of Directors of the National Alliance for the Mentally Ill (NAMI), he was the principal author of their 1997 Code of Ethics for enrolling mentally ill in research.

Dr. Shamoo's involvement in public service spans over twenty years. He has been president of the Board of Directors of Howard County Mental Health Authority (HCMHA) since its inception in 1997. He co-led four years efforts in Maryland to pass the first and most comprehensive Mental Health Parity Law in the nation in 1994.

In addition to serving on the HCMHA Board, Dr. Shamoo currently also serves as a member of the Board of Directors of Friends Research Institute, a national research and philanthropic organization, Citizens for Responsible Care and Research (also serves as first Vice-president). In the past, he had served on numerous Boards and councils at the local, state, and national level.

Dr. Shamoo is the founder and Editor-in-Chief in 1988 of the journal "Accountability in Research." He has given talks on these topics worldwide. Dr. Shamoo has held visiting professorship in notable institutions such as Institute for Political Studies in Paris, France and East Carolina University. His current interests in the area of Ethics, Science, and Public Policy are in: development of good research practices, ethics and public policy, objectivity and conflict of interest, and the use of humans in research especially persons with mental illness. Dr. Shamoo teaches graduate students on "Responsible Conduct of Research" and hold workshops on ethics in research. Dr. Shamoo has been cited and/or appeared frequently in local and national media in print, radio, and television such as The New York Times; The Boston Globe; The Dallas Morning News; The LA Times CBS; CNN as well as The Baltimore Sun and local television.

Mr. MICA. I would now like to recognize Ms. Sherry Grenz. She's with National Alliance of Mentally Ill. You are recognized.

Ms. GRENZ. Thank you. I'd also like this to become part of the official record.

Mr. MICA. Your entire statement will be made part of the official record without objection.

Ms. GRENZ. I apologize for leaving out the names of the dignitaries. I just heard about these hearings about 2 days ago on the Internet, so once again, I apologize if I left anybody's name out.

My father recently died from a stroke and he developed depression during these last painful years of his life. My mother has Alzheimer's type disease. My uncle is mentally retarded, and my brother suffers from schizophrenia. I am a primary caregiver for all. So given my family background, you can certainly see why research is so very important to me.

I am the first vice president of the National Alliance for the Mentally Ill of New York State, the largest family consumer organization in the country. We have tens of thousands of members nationally, more than 8,000 in New York State alone. I am president of the Albany chapter, and I was also the only citizen advocate to serve on the New York State Department of Health's work group charged with developing research recommendations for protected classes. The months I spent as a member of this prestigious DOH task force gave me the opportunity to learn in detail about ethical issues of research with persons too incapacitated to give consent themselves. It also sensitized me to the enormous variety of ways in which ethical issues present themselves in research studies.

I was particularly interested to learn that many of our mentally ill loved ones feel quite strongly about participating in research studies, so future generations don't have to suffer as they have. You know just because someone is mentally ill doesn't mean they are incapacitated all the time and incapable of being altruistic like many others of us in the population. So I come here not only with a deep commitment to helping those who are mentally incapacitated, but with a solid background of knowledge in trying to deal with these complicated issues as well.

I want to emphasize that I am not a professional and I am not speaking on behalf of any group or person other than myself. Now, let me just briefly share with you a story about my brother. I call him Steven in the testimony but that's not his real name. I assume that's acceptable, right? Yes, he did. Well, Steven was a handsome, outgoing young man who was so smart that he skipped 2 years in school. He was on the school football team and liked by his teachers and peers alike. His future looked bright and promising.

However, while Steven was still attending college we noticed a startling change in his personality. He insisted that people were staring at him and making derogatory remarks behind his back. Well, things quickly started to unravel after that. Many months and many doctors later we were told that Steven suffered from one of the most serious mental illnesses known to man, paranoid schizophrenia. Our hearts were broken. His life was destroyed. For the next 25 years, Steven was in and out of hospitals, lived on the streets of New York City where he was often beaten and robbed, and lived a life that was controlled by the terror and the demons

in his head. His future looked bleak. Then about 7 years ago I received a call from my parents who were living in Queens at that time telling me that Steven said he could not take it anymore and would be willing to go to a hospital if I could find a place that would treat him with dignity and give him a chance at a better life. He had heard that there was some promising medications out here, ones with less unpleasant side effects. He was desperate and so were we.

Through my years in NAMI, I gained a wealth of people to network with, and as I called around and found out more information, it was suggested that I call this facility that had a wonderful reputation with NAMI folks, the New York State Psychiatric Institute, PI. Many NAMI people told me of their positive experiences with this institute, but I decided to find out for myself to be sure. Well, after days of filling out endless forms and participating in many interviews, Steven was hospitalized in the schizophrenia research unit at PI and enrolled in a research protocol. For the first time in years we dared to hope again.

Steven received a thorough mental health workup as well as an outstanding physical workup. Sadly, families have found out that once our relatives are diagnosed with a mental illness and get into the system, their general health care is often neglected, leading to a significantly shorter life expectancy and this fact has been substantiated by those having done research on this matter. What this extensive health workup turned up was something we never dreamed of. Steven had a tumor on his kidney and it was cancerous. We were shocked. Specialists were called in and informed us that there was no choice but to operate, but Steven refused. In a psychotic state, he proclaimed he would only agree to surgery when he felt the pain of the advancing cancer. The oncologists and psychiatrists explained to him that by the time he felt this pain it would be too late, the cancer would have spread to his spine, but Steven still refused to cooperate.

Out of desperation I came up with the idea that perhaps if we gave Steven something as innocuous as Epicac, the stuff that you gave to kids to make them throw up, he would be convinced that he was sick enough and agree to the surgery. Well, PI adamantly refused to allow such a plan to take place, of course, but they continued to spend endless hours with Steven patiently explaining to him the seriousness of his situation. They also spent many hours with me and with my parents, compassionately offering us the support and information we needed.

Then 1 day miraculously Steven agreed to the surgery. The surgeon found that the cancer on his kidney was totally encapsulated and removed the kidney. Chemotherapy was not needed. The point I was making is that the thorough work of the physicians at PI literally saved Steven's life and that none of the many doctors that Steven had seen on a regular basis over the years even picked up on this problem.

Sometime after that, Steven was readmitted to PI, tried on Clozapine, a new type of medication that was discovered through research only a few short years ago and joined the world of the living once again. All is thanks to the wonders of research and the dedication and medical excellence of those at PI.

You know, I would like to quickly add something else to the testimony at this time that I think is very important. In light of the outstanding treatment my brother received at PI, I was really shocked to see the horrendous story that appeared in the New York Post. What the Post reported was really in total contrast to what my family and many other NAMI families experienced and believe me, I would never, ever support any person or research institute that conducted research in an unethical, dangerous, or cruel manner. What compassionate person would? I even tried calling the Post on several occasions to give them my perspective and share several NAMI families' experiences with them, but curiously my calls were never returned.

As a member of the DOH task force on protected classes I received a report from OPRR which they addressed here saying that these New York Post allegations were unfounded and untrue. As I understand it, and it's been confirmed they even went on to say that the research being done at PI is to be of the highest caliber, so I'm still struggling to find out what this is really all about.

Well, to wrap it up, the story of my brother's positive experience participating in a research program of PI is of course my own personal story, but I don't think it's unique.

Of course we must always strive for the highest of standards, particularly when it comes to vulnerable populations and we advocates have to be ever vigilant to be sure that all research studies are done in the safest way possible with the least risk possible and the truth is that in any profession, be it judges, lawyers, doctors, even legislators, there is an occasional negative experience or bad apple that surfaces, but it's not reasonable to paint every one in every given profession with the same brush. Mistakes should not and must not be ignored, but let's not throw out the baby with the bathwater.

Where would we be without the benefit of research; all research, cancer, diabetes, heart disease et cetera. After all, who of us has not had a beloved family member or friend who has been stricken with one of these devastating illnesses? Please remember, research is our hope for the future. Thank you.

Mr. MICA. Thank you for your testimony.

[The prepared statement of Ms. Grenz follows:]

CONGRESS OF THE UNITED STATES

House of Representatives

Committee on Government Reform
Subcommittee on Criminal Justice Drug Policy, and Human Resources

Honorable John L. Mica, Chairman

TESTIMONY PRESENTED BY
Sherry R. Grenz

December 9, 1999

Good Morning. My name is Sherry Grenz and I want to thank the Honorable John Mica, Chairman of this committee, other distinguished members, and Sherre Branson for giving me the opportunity to testify today. I am truly most appreciative.

My beloved father who recently died from a stoke, developed depression during these last years of his life; my mother has alzheimer's-type disease; my uncle is mentally retarded; and my brother suffers from schizophrenia. I am the primary caregiver for all. Given my family background, you can see why Research is so very important to me.

I am the 1st Vice-President of the National Alliance for the Mentally Ill of New York State (NAMI-NYS), the largest family/consumer organization in the country. We have tens of thousands of members nationally, more than eight thousand in New York State alone. I am President of the Albany Chapter of NAMI-NYS. I was also the only citizen advocate to serve on the New York State Department of Health's Work Group charged with developing Research recommendations for Protected Classes.

The months I spent as a member of this prestigious DOH task force, gave me the opportunity to learn in detail about ethical issues of research with persons too incapacitated to give consent themselves. It also sensitized me to the enormous variety of ways in which ethical issues present themselves in research studies.

I was interested to learn that many of our mentally ill loved ones feel strongly about participating in research studies so future generations don't have to suffer as they have. Just because someone is mentally ill, doesn't mean they are incapacitated all the time and incapable of being altruistic like others in the population!

So...I come here with not only a deep commitment to helping those who are

mentally incapacitated, but with a solid background of knowledge in trying to deal with these complicated issues, as well.

I want to emphasize that I am not a professional and I am not speaking on behalf of any group or person, other than myself.

Let me briefly share with you a story about my brother:

Steven was a handsome, outgoing, young man who was so smart that he skipped two years in school; he was on the school football team and liked by his teachers and peers alike. His future looked bright and promising. However, while Steven was attending college, we noticed a startling change in his personality; he insisted that people were staring at him and making derogatory remarks "behind his back". Things quickly started to unravel after that. Many months---and many doctors later---we were told that Steven suffered from one of the most serious mental illness know to man...Paranoid Schizophrenia. Our hearts were broken--his life was destroyed.

For the next twenty-five years, Steven was in and out of hospitals, lived on the streets of New York City (where he was often beaten and robbed), and lived a life that was controlled by terror and the demons in his head. His future looked bleak.

Then about seven years ago, I received a call from my parents telling me that Steven said he "could not take it any more" and would be willing to go to a hospital if I could find him "a place" that would treat him with dignity and give him a chance at a better life. He had heard that there were some more promising medications out there; ones with less unpleasant side effects. He was desperate---so were we.

My years in NAMI gave me a wealth of people to network with and it was suggested that I call a facility that had a wonderful reputation with NAMI folks--New York State Psychiatric Institute(NYSPI). Many NAMI people told me of their positive experiences with the institute and I decided to find out for myself.

After days of filling out endless forms and participating in many interviews, Steven was hospitalized on the Schizophrenia Research Unit at NYSPI and enrolled in a research protocol. For the first time in years, we dared to "hope" again.

Steven received a thorough mental health workup, as well as an outstanding physical workup. Sadly, families have found that once our relatives are diagnosed with a mental illness and get into the "system", their general health care is often neglected, leading to a significantly shorter life expectancy. (This fact has been substantiated by those having done research on this matter.)

Well---what this extensive health work-up turned up, was something we never dreamed of...Steven had a tumor on his kidney--it was cancerous! We were shocked. Specialists were called in and informed us there was no choice but to operate. Steven refused! In his psychotic state, he proclaimed he would only agree to surgery when he felt the pain of the advancing cancer. The oncologist and psychiatrists explained to him that by the time he felt this pain, it would be too late, the cancer would have spread to his spine. Steven still refused to cooperate. Out of desperation, I came up with the idea that, perhaps, if we gave Steven something as innocuous as Ipecac to drink (the stuff that makes you want to throw up), he would be convinced he was sick enough, and agree to the surgery.

NYSPI adamantly refused to allow such a plan to take place, of course, but, they

continued to spend endless hours with Steven, patiently explaining to him the seriousness of the situation. They also spent many hours with me and my parents compassionately offering us the support and information we needed. Then one day, miraculously, Steven agreed to the surgery.

The surgeon found that the cancer on his kidney was totally encapsulated and removed the kidney. Chemotherapy was not needed. The thorough work of the physician's at NYSPI literally saved Steven's life! None of the many doctors that Steven had seen on a regular basis over they years, even picked up on this potentially fatal disease.

Some time after that, Steven was readmitted to NYSPI, tried on clozapine, a new atypical medication that was discovered through research only a few short years ago, and joined "the world of the living" once again! All this thanks to the wonders of research---and the dedication and medical excellence of those at NYSPI.

I would like to add something to this testimony at this time that I think is very important. In light of the outstanding treatment my brother received while he was a patient at NYSPI, I was really shocked to see the horrendous stories that appeared in The New York Post. What The Post reported, was totally in contrast to what MY family, and many other NAMI families experienced. And please believe me, I would never, ever support any person or research institute that conducted research in an unethical, dangerous, or cruel manner! What decent, compassionate person would?! I even tried calling The Post on several occasions to give them my perspective and share several NAMI families experiences with them, but, curiously, my calls were ever returned.

As a member of the DOH task force on protected classes, I also received a

report from The Office of Protection for Research Risks who carefully investigated these New York Post allegations and found them to be totally untrue. As I understand it, they even went on to say that the research being done at NYSPI to be of the highest caliber. So, I'm still "struggling" to find out what this is all really about.

The story of my brother's positive experience with participating in a research program at NYSPI is, of course, my own personal story. But I don't think it's unique. I know many other NAMI families who have had relatives at NYSPI and have only the highest of praise for this institute.

Of course, we must always strive for the highest of standards, particularly when it comes to vulnerable populations; and we advocates have to be ever vigilant to make sure that all research studies are done in the safest way possible with the least risk possible. And the truth is that in any profession---be it Judge's, Lawyers, Doctors or even Legislators---there is an occasional negative experience or "bad apple" that surfaces. But it's not reasonable to paint everyone in any given profession with the same brush. Mistakes should not---and MUST NOT--be ignored, bet let's not "throw out the baby with the bathwater"!

Where would we be without the benefits of research...ALL research: Cancer, heart, diabetes, mental illness, etc.? After all, who of us has NOT had a beloved family member or friend who has been stricken with one of these devastating illnesses? Remember---

RESEARCH IS OUR HOPE FOR THE FUTURE

Ms. Sherry Grenz

National Alliance of Mentally Ill

Q: Do you or your organization have specific or model recommendations for conducting human subject research? For how IRBs should operate?

Q. Does you organization have an opinion of the role of Federal and State governments in regulating human subject research? What role can professional organizations and associations, such as yours, play?

Q. Do you feel that human subject research issues and the need to protect participants are matters of increasing importance in this age of gene research and other new medical and scientific developments?

Mr. MICA. We'll now hear from Ms. Charisse Johnson of Brooklyn, NY. Welcome, and you're recognized.

Ms. JOHNSON. Thank you, Mr. Chairman, and committee members who extended this invitation to me to testify at this public hearing——

Mr. MICA. If you could pull that mic up as close as possible.

Ms. JOHNSON [continuing]. "Do Current Federal Regulations Adequately Protect People who Participate in Medical Research?"

If my family's experience is taken into consideration, then there are really no protections for people like my family from the outrageous behavior for some researchers who are supposed to be regulated by State and Federal laws. How else can you explain the use of children as young as 6 years old by researchers? How did they decide that he and 33 other healthy African-American and Hispanic boys were perfect subjects for the experimentation for the dangerous drug fenfluramine?

As you're aware, fenfluramine is the dangerous half of fen-phen, a diet drug taken off the market because it causes heart valve damage in adults. I later learned that these researchers specifically set out to experiment with African-American and Hispanic children while excluding white children.

My involvement with this nightmare experience started in 1992 when my 16 year old son became a first time juvenile offender. I did not know how the juvenile justice system worked or exactly what to expect. A few months after my 16 year old son was sentenced to juvenile detention I was contacted by experimenters. They requested my involvement in a study being conducted at the New York Psychiatric Institute Columbia University by Danny Pines and Gail Wasserman and other experimenters.

At first I did not understand how and from what source they obtained my name and knew I had a 6-year old son. I later came to the conclusion that this information came to them because of my 16 year old son's involvement with the juvenile justice system. Needless to say, I decided to cooperate with the experimenters. I felt at the time that if they could find me and knew I had a 6-year old son they had enough power to affect the well being of my 16 year old son who was being held in a detention facility.

This started a series of visits by my 6 year old son and myself to the campus of Columbia University, where we were subject to a series of intimate, degrading questions, tests and interviews. The experimenters also took advantage of my fear for the well-being of my 16 year old son to intrude on my privacy of my home.

Sometime in 1994 the experimenters Pine and Wasserman and the team decided it was time to take off the kid gloves and give the drug fenfluramine to my son, who was a normal healthy happy go lucky child until that day. Since being given fenfluramine by experimenters, my son and my family have suffered tremendously and continue to suffer.

About 2 weeks after he was given the drug he started having sharp painful headaches. Then as the headaches became more unbearable, he started having anxiety attacks and hyperventilating. He would start gasping for breath as if he couldn't breathe, as with someone who was having an asthma attack.

I then imagined that maybe he had asthma and took him to the doctor. The doctor after completing tests on him concluded that he did not have asthma. Nonetheless, the headaches, the anxiety attacks and the hyperventilating continued. Later his condition would only get worse. He started having horrible nightmares. He would wake up in the night screaming, thinking that someone was in his room. To this day my son continues to suffer the severe consequences of the reckless disregard for him as a human being by these experimenters. To them he was just another guinea pig.

It may be asked by some why would you participate? I would answer the question by posing a question of my own. If you were in my position, had a son who was a first time offender in the juvenile system and out of nowhere people started writing you for information about your family, maybe you think that they had enough power to affect the well-being of your son who was locked up in the juvenile facility, what would you have done? If they did not give you a true explanation of the drug fenfluramine, if you had never heard of such a drug, if they also presented themselves as doctors who you have been thought to think only act in the best interests of you and your family, if they are operating out of the well known institution of Columbia University, I suspect that a lot of parents would be likely to cooperate with these seeming good doctors not knowing that they may be dealing with Dr. Jekyl and Mr. Hyde.

At the end of these experiments, they did not have the human decency to admit that my son was used as a guinea pig for their selfish purposes. Requests by my attorneys for my sons records were met with refusals for 9 months. It was only after the involvement of the dedicated staff membership from the congressional committee office that the records of my son's experiments were finally realized. The records confirm that the nightmare experience was indeed a nightmare. Thank you.

Mr. MICA. Thank you for your testimony.

I'd like to thank all of our witnesses on this panel. A couple of quick questions.

Mr. Zucker, you have reviewed the recommendations of the Bioethics Advisory Commission for protecting human subject research involving mentally ill patients. Do you have any additional recommendations other than what you provided us with?

Mr. ZUCKER. We may be able to provide you with some additional recommendations. And I can, if I could take the liberty of submitting an additional statement.

Mr. MICA. Would you recommend that these be instituted by statute or by regulation?

Mr. ZUCKER. I think that it is important that the Congress act and enact statutes. First recommendations were imposed by the Belmont commission, they were proposed and they were defeated; there were special protections for other vulnerable groups. I am afraid in 20 years from now if the Legislature does not act, then we will be looking back at the impact of the Board in an unfavorable light.

I think there are some key principles that the Congress could enact and I've made some proposals in my written testimony along those lines.

Mr. MICA. Thank you. Dr. Shamoo, one of the members, I read the entire testimony but one of the Members' remarked sort of echoed yours in this June hearing over a year ago, that rodents, he said, had more protections than human beings, and you sort of echoed that in your testimony.

You also said that some of the protections that are in law for an animal you could substitute human being. Would that in fact be adequate or would you certainly have to massage other language?

Mr. SHAMOO. Absolutely. I was sincere in that comparison. It was the first time I gave written testimony to 1995, I mentioned those facts. For example, in animal research, there is monitoring, there is audit at this time, there is inspection of the facilities. None of that exists for human beings, and the most important difference, that no matter what site of research is, who the source of funding, anywhere in the United States, you must comply with the Federal regulations. That is not the case, and I don't know what the percentage is, but I will guesstimate somewhere around 30 to 40 percent of all human subject experiments are not subject to any regulations in this country.

Mr. MICA. Dr. Zucker, you said I think the Bellevue case, where you had sought to file a complaint with OPRR and that they said they had no jurisdiction. There's no other source for you to appeal to? Or can you file a complaint?

Mr. ZUCKER. They referred the matter to the Food and Drug Administration.

Mr. MICA. They did.

Mr. ZUCKER. They did. It's unclear to me what has happened to the complaint in the Food and Drug Administration because it's my impression this is not the sort of investigation they normally conduct. We are also pursuing a complaint with the New York State Department of Health.

Mr. MICA. So at the Federal level, you feel there's inadequate overall jurisdiction, and that should be specified by law?

Mr. ZUCKER. I think so. OPRR does have, I think it is the agency within the Federal Government with the most expertise in overseeing the operation of institutional review boards, and it seems ridiculous to expect FDA to replicate that expertise within the FDA.

Mr. MICA. It seems to be it would be better to have the most expert agency review complaints of this nature.

And I would imagine both of you, dealing with either children or mentally ill individuals, would want to have some extra protections instituted or legal procedures that would be closer to follow, is that correct?

Mr. ZUCKER. That is correct. In my written testimony I propose some statutory language and I'd be happy to work with your staff to fine tune that or to develop that.

Mr. MICA. I thank you both. I yield now, if I may, to Mr. Towns.

Mr. TOWNS. Thank you very much, Mr. Chairman. Let me thank all of the witnesses for their testimony. It was very enlightening. Let me ask you too, Mr. Zucker, in your testimony, you noted that the definition of the word "condition" was a pivotal concern in OPRR's failure to discipline New York State Psychiatric Institute. Could you elaborate on why the redefinition of the word "condition"

as used in this decision would serve as a dangerous precedent in the future?

Mr. ZUCKER. I think so. I mean, to really understand this, I think you have to contrast what OPRR said and did with the research that was occurring at Mt. Sinai and the results that were reached at PI, which are very hard to reconcile. Mt. Sinai was sharply criticized for putting so-called normal control children in a fenfluramine challenge, because it was said these children did not have a condition, and therefore, it was wrong to subject these children to the risks of a fenfluramine challenge.

OPRR then turned around and said that it was OK to subject the children—the young minority boys at the Psychiatric Institute to the very same risks, because they were not normal controls, they were poor children who had an older brother who was a juvenile delinquent and some people thought maybe their parents weren't such great parents.

That was the criteria. In a city like New York, I mean, they said it themselves. 90 percent, 98 percent I believe PI says of the children in the juvenile delinquent system in New York City are apparently minority children, so that if the law can be interpreted the way OPRR is now interpreting it, it means that minority children in New York don't have the same protections as middle class children who don't, presumably will not be labeled as coming from an adverse child rearing environment, and I don't think we want to create a two-tiered, class-based system that has a disparity impact on race in the major cities that after all where is this research primarily occurring, it's occurring in New York, Chicago, Los Angeles, in cities which large minority populations and where there's going to be a disproportionate number of minority kids found in the juvenile justice system.

So I think Congress has to say that as a matter of public policy, this is not an acceptable interpretation of Federal law, that if you can't do this to middle class kids who may be largely white in a lot of communities, then you can't do it to poor children who are going to be predominantly minority children in the major cities where the research occurs.

Mr. TOWNS. Thank you very much.

Ms. Johnson, let me ask you, let me begin by first, wanting to express my sympathy for the ordeals that you and your son went through, and also to commend you on coming forward to testify, because I think as a result of your testimony, I think you're going to save a lot of folks some pain and agony as a result of your stepping forward and to share that which happened to you.

As to the side effects that your son has experienced since his participation in the experiment, has your son been offered any treatment or assistance by the researchers? Talking about the New York State Psychiatric Institute or anyone affiliated with the organization.

Ms. JOHNSON. No.

Mr. TOWNS. I was concerned about the way in which you and your son were recruited as well. I thought that the juvenile court records were supposed to be confidential records.

Ms. JOHNSON. Right.

Mr. TOWNS. That was my impression.

Ms. JOHNSON. Mine, too.

Mr. TOWNS. Purely by releasing the names of you and your son to researchers, the confidential nature of those records, I think was breached. Were you ever told by the researchers, by the juvenile court or family court or any of the authorities that if you refused to participate, that refusal would in no way affect the case of your older son who was in the juvenile detention facility, were you ever told?

Ms. JOHNSON. No.

Mr. TOWNS. They never told you that?

Ms. JOHNSON. No.

Mr. TOWNS. So you probably just sort of felt it was important to cooperate, because you wouldn't do anything to further bring about harm to your older son.

Ms. JOHNSON. Sure.

Mr. TOWNS. Were you afraid that by coming forward you would place your older son in jeopardy, that you felt if by not coming forward, that would be a problem?

Ms. JOHNSON. That's what I felt.

Mr. TOWNS. So that's like a little form of intimidation.

Representatives of the New York Psychiatric Institute have testified that the overwhelming majority of children in the study had behavioral problems. Did your son have any kind of behavior problems before he participated in the study?

Ms. JOHNSON. None whatsoever, no.

Mr. TOWNS. Were you told at any point in time that your son, who was 6 years old at the time, that the drug they were going to put him on had never been tested with anyone under the age of 12, never been tried on them at that time, were you told that?

Ms. JOHNSON. No.

Mr. TOWNS. Well, let me just say, Mr. Chairman, I think this further points out that we have to act in Congress in order to make certain that people are protected, and that I think the only way we could do that is by legislation, I think if we leave it out there loosely, I don't think the protection that's needed will come about.

So I want to thank you very much for sharing and also to say also to Ms. Grenz that I really appreciate your coming forward and sharing as well, because here you have several situations wherein you feel yourself responsible for and I think that people might not be able to make the decision as to whether or not they should be involved in a research kind of setting, and you would be called upon, and I think being called upon to make those kinds of decisions without having all the information is not fair.

So whether it's in your case, I think that you point out to us that you need to have information in order to be able to move forward, and I got that from your testimony, that it's important to have this data so you could make the decision as to what should happen from that point on.

I guess the last one I sort of wanted to throw out there, Mr. Chairman, I guess that this is for Mr. Zucker. In your testimony you discuss washout. Do you believe that washout should be banned?

Mr. ZUCKER. I think that would go too far, but I do think that washouts and placebos involve significant risks that are not thera-

peutic risks, and again, to bring it back to the situation at the Bellevue New York University School of Medicine study, there I think it was inappropriate there, because you had people who were coming into the hospital, histories of suicidal and other violent behavior, who either came to the hospital or were brought to the hospital because they were really in a psychiatric crisis and potentially dangerous, that to take those people and then put them on a placebo or just to wash them out of any medication and not to offer them care during that period, I think is unethical, because patients who come to the psychiatric hospital in crisis reasonably expect care.

I think that they will have a very hard time understanding that it is a delusion, kind of a therapeutic delusion that when the doctor says would you like to participate in this experiment, that he's offering them something which is not in their best interests, which may allow them to suffer for weeks.

There was a potential here. Everyone got a 1-week washout, and then some people were put on a placebo, and so continued to receive no medication and others did receive the experimental drug or another drug.

Under those particular facts, I believe it is unethical to offer a washout and a placebo before you determine that you can't help this person using nonexperimental treatments that are readily available.

Mr. TOWNS. Thank you. Thank you very much, Mr. Chairman. I really appreciate your coming to New York and having this hearing. I think it means a lot to a lot of people, because I think there's more going on, Mr. Chairman, than we really realize. I think that we feel the situation here, we read about an incident that occurred maybe in the newspaper, but I think that there's a lot more going on. I think that we have to sort of make certain that we put legislation into a new form, legislation that's going to help people, and I think there's a definite need to do that.

When you think of a youngster 6 years old being put on a drug that not even the pharmaceutical company tested to find out whether or not it would do harm to anyone under 12, I mean, that to me is just something that should not happen in the United States of America, and Mr. Chairman, I think we have an obligation and responsibility to so provide.

Mr. MICA. I thank the gentleman from New York for his persistence on this issue, and his leadership in Congress on this and many other issues, and I'm pleased to state that I've had the opportunity to work with him for many years, and we, when our side was in the minority, I've often cited Mr. Towns' respect for the minority and working with me as a Member at that time, in fact, I came in as a junior in Congress, and the respect with which he treated me, I thank him for that publicly and personally. And also for again his leadership on this issue.

It is important that we fulfill our congressional responsibilities and oversight, as I said, and also legislatively to see that we have in place the adequate protections both under statute and regulation. We'll work with the administration to see the kinds of things that can be put into place and are put into place and don't have foot dragging on an area that's so important and where the public

needs to be protected, not only the public at large, but particularly children, mentally ill and others who society must protect, so hopefully we can use this as a constructive basis to proceed and I know that knowing Mr. Towns very well, we will have additional follow-up to this inquiry that's taken place in New York today.

There being no further business to come before this subcommittee, this meeting of this Subcommittee on Criminal Justice, Drug Policy, and Human Resources is adjourned.

[Whereupon, at 2 p.m., the subcommittee was adjourned.]

[Additional information submitted for the hearing record follows:]

New York State Psychiatric Institute

Established 1896 — *Over a Century of Excellence in Research, Clinical Care and Education*

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Deputy Director

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JOHN M. OLDHAM, MD, Director

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Deputy Director for Administration

January 13, 2000

The Honorable John L. Mica
Chairman
Subcommittee on Criminal Justice, Drug Policy, and Human Resources
Committee on Government Reform
United States House of Representatives
2157 Rayburn House Office Building
Washington, D.C. 21515-6413

Dear Representative Mica:

In response to your letter of December 16, 1999, I appreciate the opportunity to answer the follow-up questions pertaining to the field hearing held on December 9, 1999:

1. In your testimony you note that the children involved in the study have "behavioral problems." Yet you do not state that these so called behavioral problems were the result of mental disorders. Was there ever a finding that all of the children in this study had a specific mental disorder?

Federal regulations did not require that the children in this study have a specific mental disorder, although, in fact, at the time the fenfluramine study was carried out, 30 (88%) of 34 did. Rather, federal regulations provide that research proposing to involve children in studies that involve a minor increase over minimal risk and no prospect of direct benefit may only be conducted if the IRB determines that, among other things, "the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition." 45 CFR 46.406 (emphasis added). As OPRR found in its report, the fenfluramine research was conducted in accordance with this requirement of the federal regulations. The children in this study were all at high risk for the development of mental disorders, a "condition" within the meaning of the regulations.

Most had already developed a mental disorder. Specifically, as described in the paper published in 1997, clinical status was assessed in two ways: on the basis of an interview with the parent and on the basis of a standardized questionnaire completed by the parent. According to the interview, 22 (65%) of 34 met criteria for a Disruptive Behavior Disorder or an Anxiety Disorder (these data are reported in the paper). In addition, based on the interview, 5 other boys met criteria for other mental disorders. On the basis of the questionnaire, 23 (68%) of the 34 boys met criteria for a mental disorder. In total, 30 (88%) of the 34 boys met criteria according to one or both of these measures.

NYS Office of Mental Health - An Equal Opportunity / Affirmative Action Employer

2. You testified that the study provided important treatment strategies.

- *What were these strategies?*
- *Have you done any follow up to determine whether the children involved in the research benefitted from these treatment strategies?*

The broad aim of the research program, of which the fenfluramine study was a part, was to identify familial and environmental factors that might be targets for interventions designed to reduce the chances that at-risk children will develop behavioral problems. The study identified three areas of parent-child interaction which appear to be especially important: decreasing parent-child conflict, increasing positive parent-child involvement, and increasing supervision. The fenfluramine study indicated that such interactions may lead to changes in brain functioning which are associated with fewer behavioral problems. The results of the fenfluramine study emphasized the significant relationship between a positive home environment and a measure of brain serotonin, and thereby directed attention to important areas of child care that might be usefully targeted for intervention. Programs designed to help parents take advantage of these methods in raising their children are now being actively studied, both across the country and, as described in response to question 4 below, in New York City.

The participants in this study did not receive these interventions because the interventions were only devised after the study had been completed and the results were analyzed. However, at the time, referrals for mental health services were provided where parents reported behavioral problems and indicated an interest in such services. When medical and academic problems were identified, appropriate referrals were also made.

3. Did New York Psychiatric Institute or the State Office of Mental Health ever conduct an investigation or put forth a report concerning this particular trial? If so, please provide the subcommittee with a copy of this report.

In January, 1998 OPRR requested an investigation of allegations of noncompliance with Health and Human Services (HHS) regulations for the protection of human subjects relating to the fenfluramine study. In response to this request, an extensive investigation of the study and its review by the IRB was conducted under the direction of Heinz E. Lehmann, M.D., Deputy Commissioner for Research, New York State Office of Mental Health, and John M. Oldham, M.D., Director of New York Psychiatric Institute. The report of this investigation and its extensive back up documentation was submitted to the Research Foundation for Mental Hygiene, Inc. and reviewed by the Managing Director and Clinical Research Coordinator prior to being sent to OPRR on February 27, 1998. The documentation submitted to OPRR consisted of the report, a chronological summary of the IRB review and approval process, copies of all relevant research protocols, informed consent documents, IRB minutes, correspondence, continuing review reports and associated documents.

As the OPRR investigation continued, additional information was provided to OPRR in response to questions raised. The subcommittee has previously been provided with copies of the materials submitted to OPRR. However, for your convenience, a copy of the initial report is attached.

4. Please submit to the committee all information concerning the Department of Education grant that you reference in your testimony.

The results of the overall research study, including the fenfluramine study, helped provide a foundation for ongoing research, both at NYPI and elsewhere, which aims to assist parents to raise their children under difficult circumstances. A specific example is the ParentCorps program.

ParentCorps is a new initiative of the Institute for Children at Risk of the New York University Child Study Center to strengthen families of preschoolers from socioeconomically disadvantaged communities through parent-to-parent networks, scientifically-based practices and state-of-the-art technology. The goal is to promote child social and academic competence and prevent mental health problems, school failure and juvenile delinquency by strengthening parenting practices, enhancing parents' ability to advocate for their young children, and empowering parents to access resources in their own communities. The parenting practices that are targeted by this program are similar to those found to be important predictors of later development in the research program of which the fenfluramine study was a part.

The ParentCorps program, initiated in October 1999, is currently being developed in partnership with several community-based organizations, to ensure that all ParentCorps programs and materials are designed and provided in a way that is sensitive to the needs of the families served by the program, and is consistent with the goals of the community. Parents and community leaders are actively involved in the design, implementation and ongoing evaluation and refinement of all aspects of the program.

The successful nation-wide implementation of ParentCorps requires three key phases: Phase 1: Development and Feasibility Study; Phase 2: Effectiveness Study; Phase 3: Dissemination. ParentCorps is currently in the first phase of development, with funding from the Fund for the Improvement of Education of the U.S. Department of Education, as well as corporate and foundation support. During Phase 1, the program will be pilot tested in a well-defined neighborhood in Central Harlem. Based on the results from the Phase 1 Feasibility Study, the investigators hope to apply for funding for a multi-site effectiveness trial to test the ParentCorps program in communities in different parts of the country.

In closing, I would like to correct any confusion which may exist as to Dr. Timothy Walsh's testimony regarding the racial composition of the participants in the fenfluramine study. As Dr. Walsh told the Committee, all of the participants in the fenfluramine study were African-Americans or Hispanics. There was no conflict or inconsistency in Dr. Walsh's June 1998 testimony before the Subcommittee on Human Resources. In both hearings, Dr. Walsh testified--consistent with the facts--that (1) the IRB had never approved a racial exclusion for either the overall research study OR for the fenfluramine substudy, and (2) there were only a few non-minority participants in the overall study, reflective of the population from which they were drawn. There was no racial bias in either study's design or intent--to learn more about the development of anti-social behavior in young boys at high risk for developing such problems. The ethnic distribution of the families who participated in these studies simply reflected the ethnic distribution of the families whose names were provided to the investigators by the juvenile court systems in the Bronx and Manhattan.

We truly appreciate the committee's interest in this area and the opportunity to address your questions. Please let me know if you would like any further information.

Very truly yours,

John Oldham, M.D.

February 27, 1998

SUMMARY REPORT

Protocol #2282:	MEDICAL AND NEUROLOGICAL ASSESSMENT IN A POPULATION AT RISK FOR ANTISOCIAL BEHAVIOR Dr. Michael Liebowitz Dr. Gail Wasserman/Dr. Dan Pine

The article, "Neuroendocrine response to Fenfluramine Challenge in Boys," 54 Arch. Gen. Psych. 839 (September 1997) reported the results of one portion of a larger systematic research project, "Medical and Neurological Assessment in a Population at Risk for Antisocial Behavior" (IRB #2282). The purpose of the research project was 1) To identify predisposing medical, neurobiological, neurological, neuropsychological, psychiatric and behavioral factors in a population at risk for the development of antisocial behavior, a serious conduct disorder for which no effective treatment is currently known; 2) to seek physical and psychological factors that might allow preventive interventions; and 3) to implement prevention procedures in this high risk population. All subjects were siblings of children who had been adjudicated juvenile delinquents and were considered at high risk for the development of antisocial behaviors.

The portion of the study reported in the article must be considered in the context of the larger study that the children participated in. For example, while it is correct that the fenfluramine challenge did not provide any benefit to the participants, each child received a number of health related benefits from the study as a whole. Specifically, each child received a comprehensive medical, behavioral and cognitive evaluation designed to detect learning, emotional or medical problems. It was anticipated that a significant proportion of the total subject population would have undiagnosed problems. In fact, two thirds of the children whose results were reported in the article exhibited clinically significant (i.e., requiring treatment by a medical or mental health professional), but previously undiagnosed, medical or behavioral problems.

When problems were detected, families were assisted in obtaining appropriate services. This included referrals to and consultations with physicians, therapists counselors and school officials and provision of services by professionals at the New York State Psychiatric Institute (NYPI). Although not part of the research project per se, interventions were implemented by staff of NYPI to treat emerging conduct problems.

Initial and ongoing review and monitoring of study 2282 was conducted by the NYPI IRB (Assurance M1376, IRB #01). As shown by the chronology and documentation of the IRB review process included with this submission, the IRB conscientiously carried out its responsibilities in a lengthy process that included many subcommittee reviews in addition

to the full board reviews. Extensive documentation in support of the application was required, consultants were used, and, following approval, investigators were required to provide progress reports to the IRB. For example, on 4/27/93 the IRB approved continuing recruitment into the larger study based on documentation of the parents assessment of their children's recruitment experiences. Similarly, on 10/26/94 and 12/15/94 the IRB reviewed the experiences of subjects who had participated in the fenfluramine challenge. In considering the response to study 2282 as a whole, families overwhelmingly reported the research experience as a positive one and both families and children expressed a willingness to consider future participation in such studies.

A key component of the IRB review process was constant evaluation of the federal regulations governing the inclusion of children in research, in particular section 45 CFR 46.406. Approval to conduct the study was granted in stages as the IRB considered the risk level of the various study components and the different subgroups of potential participants. Please note that although the initial application included 10 control subjects, who would not be "at risk," this subgroup did not participate in the study. As shown in the attached documentation, participation of this group of subjects would have been considered by the IRB only if it had determined that the fenfluramine challenge involved no more than minimal risk. During the time period that this study was active the IRB did not approve the procedure in the category of no more than minimal risk and, therefore, the participation of "controls" was not actively considered.

Study #2282 included multiple components. IRB approval was given in stages based upon the type of procedures involved and the specific sub-set of the subject population, all of whom where siblings of children who had been adjudicated as juvenile delinquents. The sequence of the approval process, as documented in greater detail in the chronology and back up documentation, consisted of:

1. Neuropsychological component for all subjects (no more than minimal risk).

2. MRI for all subjects (no more than minimal risk).

3. Fenfluramine challenge (minor increase over minimal risk 45 CFR 46.406) for children with a diagnosis of disruptive behavior or scoring above clinical cut off on the Achenbach scale for externalized symptoms. A diagnosis of disruptive behavior means that a child has a clinical syndrome, with features of aggressive or impulsive behavior that needs to be treated psychiatrically. A score "above the clinical cutoff on the Achenbach" means that the child has more problems in a given clinical domain than 95% of all other children living in the United States. As with a diagnosis, this means that a child is in need of clinical attention.

4 Fenfluramine challenge for all subjects approved by the IRB as a minor increase over minimal risk 45 CFR 46.406. Note that the IRB at this time considered the

possibility that the challenge would more accurately be categorized as no more than minimal risk but would not make this determination without additional information. After the conclusion of study 2282 additional information was reviewed by the IRB and a no more than minimal risk determination was made for the use of a fenfluramine challenge in another study for children aged 12-18. (Biological Studies in Suicidal Adolescents and Young Adult Inpatients - Dr. L. Greenhill).

Review of the IRB documentation supports the appropriateness of the decisions made by the IRB in approving the involvement of minors in this study. The IRB adopted the most cautious approach to the application of 45 CFR Part 46 Subpart D to the fenfluramine challenge portion of this research by reviewing it apart from the study as a whole. The potential benefits of the other components of the study were not considered in the IRB's evaluation of whether the fenfluramine component could be approved. Thus, although it may well be that the standards in 45 CFR 46.405 (more than minimal risk, prospect of direct benefit) were applicable, the IRB required the investigators to meet the higher standards of 45 CFR (more than minimal risk, no prospect of direct benefit).

Additional Issues Raised by Disability Advocates.

Several issues that go beyond the questions identified in the OPRR letter of January 26, 1998 were raised in the letter from Disability Advocates. In the interests of providing a complete response they will be addressed here.

1. Muldoon et al Article

The relevance of the study of Muldoon et al., to the Pine study is at best unclear. In addition to the fact that the Muldoon study was published in 1996, after the conclusion of the fenfluramine challenge test component of this study, the Muldoon study involved adults rather than children. Responses to pharmacologic agents by children and adults may differ, as is well known for psychostimulants.

The IRB reviewed extensive data from similar fenfluramine studies in children which indicated that the procedure was (and is) safe for children For example, Stoff et al. 1992 (copy attached) used the fenfluramine challenge to study 15 young children with behavior problems, 8 adolescents with behavior problems and 8 healthy control adolescents. In this study, only mild side effects were seen during the fenfluramine challenge. ... "some subjects reported somatic complaints that included drowsiness(50-60%), nausea (33%), headaches (33%) and lightheadedness (33%), all minor in severity." (p270)

Similarly, Dr Jeffrey Halperin and his colleagues have conducted fenfluramine challenges in more than 50 young children with behavior problems and healthy control children In a 1994 publication (attached) two of twenty five children were noted to have

side effects from fenfluramine. One had headache, nausea and vomiting, the second had headache with nausea. (p246) Based upon his continued research in young children, involving more than 50 fenfluramine challenges, Dr. Halperin provided further data on side effects to Drs. Pine and Wasserman and the IRB while study 2282 was under review. These data were consistent with the data from Halperin et al. 1994 and from Stoff et al. 1992.

Finally, it should be noted that both the study of Halperin (1994) and the study of Stoff (1992) were felt to be ethically permissible by the NIMH, based upon the fact that both studies were reviewed and funded by the NIMH (Halperin et al. NIMH-RO1-MH46448; Stoff et al. NIMH MH40364 and RSDA MH00509). Similarly Drs. Wasserman and Pine recently submitted a grant to the NIMH (1-RO1-MH 56598-01) that involved a fenfluramine challenge in a similar population. Attached is the review of this grant indicating that human subject issues are well addressed.

2. FDA withdrawal of marketing approval for fenfluramine

The fenfluramine challenge component of study 2282 was terminated in August 1995. This was more than two years prior to the 1997 FDA withdrawal of fenfluramine from the market because of its association with heart valve damage. Upon receipt of the FDA announcement, IRB chairperson B. Timothy Walsh, M.D. contacted Dr. Thomas Laughren of the FDA to discuss the continuing use of fenfluramine challenges in children and whether any follow-up evaluation should be done for the participants in ongoing or past studies. Dr. Laughren stated that heart valve damage was associated with long-term use of fenfluramine and had not been seen following single dose use of fenfluramine, therefore the FDA would continue to permit single doses of fenfluramine to be used in research studies upon satisfactory completion of the appropriate application (IND).

When protocol 2282 was first reviewed, and indeed during the entire period when the fenfluramine challenge component was active, definitive evidence of the association between fenfluramine and pulmonary hypertension was not yet available. The first sytematic epidemiological study that documented the increase risk of pulmonary hypertension associated with fenfluramine was published in 1996, after the challenge study had been stopped (Lucien Abenhaim, M.D. et.al., New England Journal of Medicine 335:609-616,1996). The risk clearly increased with chronic (more than 3 months use) but was still very low. Even today, there is no evidence that a single dose of fenfluramine increases the risk of pulmonary hypertension.

3. Selection of Poor Minority Children

The participants in Study 2282 were younger siblings of adjudicated juvenile delinquents, identified from the court records of the New York City Family Court serving Manhattan and the Bronx. These Boroughs were chosen because of their proximity to

New York State Psychiatric Institute (NYSPI). The extent of contact with the children and their mothers required by the study, both in their homes and at NYSPI, meant that it would have been difficult to study children who lived at a greater distance. Many markers of social adversity, including delinquency, tend to cluster in economically impoverished populations. New York City's disadvantaged are overwhelmingly of minority status. Family Court contact, as a consequence, is also more common among minority youth. This study sought to address serious conduct disorder, which is of grave concern to this and other communities. Indeed, participation in the study provided significant clinical resources to an underserved population.

As discussed by Wasserman et al. (1996), the demographics of the sample in Pine et al. (1997) and in Wasserman et al. (1996), are consistent with the fact that most families from Manhattan or the Bronx with a delinquent boy are economically disadvantaged and from minority backgrounds. The paper by Wasserman et al. (1996), notes that fewer than 5% of the participants of this study were other than African American or Hispanic. This study was open to families of all boys who were adjudicated as a juvenile delinquent and had a male sibling within the age range of six to ten years. The earlier Pine study cited by Disability Advocates was conducted on a sub-set of 34 children from this sample and did involve three boys who were not African American or Hispanic. The demographic limitations of the initial study that were caused by recruitment from Manhattan and the Bronx were recognized. A grant application (NIMH 1RO1 MH 56598-01) was submitted to expand the data to other ethnic groups and to include females. In this re-submission, liaisons were developed with officials in Queens where children from Caucasian and other ethnic groups are more commonly adjudicated.

Heinz E. Lehmann

Heinz E. Lehmann, M.D.
Deputy Commissioner for Research
Office of Mental Health

John M. Oldham (M.D.)

John M. Oldham, M.D.
Director, New York State Psychiatric Institute
Chief Medical Officer, Office of Mental Health

Submitted: February 27, 1998

Statement of Gregory L. Eastwood, M.D., President
Associated Medical Schools of New York (AMS)

House Subcommittee on Criminal Justice, Drug Policy and Human Resources

I appreciate the opportunity to comment on the issue of protecting people who participate in medical research, which was the subject of a Subcommittee hearing on December 9, 1999, in New York City.

Within the last couple of years, this issue has been the subject of extensive dialogue nationally, and has particular relevance in the State of New York as one of the country's major centers for medical research. The Deans of the 14 New York medical schools have made clear their position that the protection of human subjects in medical research is the highest priority concern in research. We believe that the existing federal safeguards provide assurance of such protection, but the research community bears the responsibility for compliance with these regulations.

At the core of compliance is the Institutional Review Boards (IRB), which each research institution has in place to provide assurance that human subjects in research are protected, that they are fully informed of the nature of the research project and that they consent to participate. The members of the IRBs include research faculty, ethicists and patient representatives. Medical schools typically enter into a Multiple Project Assurance (MPA) agreement with the federal Office for Protection from Research Risks (OPRR), under which all research at a particular institution is subject to oversight by the OPRR.

The track record of IRBs in carrying out their mission is outstanding; given the estimated 16,000 to 20,000 research projects conducted each year in this country involving human subjects. Instances of actual violations of federal regulations are remarkably few. Nonetheless, when any violation occurs or any instance of a lapse in the functioning of an IRB functioning, major attention must be paid to determining the cause of the problem and to ways to minimize such problems.

One concern is those research projects that are not covered by federal regulations. Most institutions apply federal guidelines to all research that they sponsor, but many studies remain outside the purview of these regulations.

In the ongoing discussions of research subject protection, one obvious fact frequently is under-emphasized. The scientists who design and carry out the research and the research itself is aimed ultimately at benefiting those who participate. Again, the medical schools give priority to the protection of the rights of research subjects, but we have serious concern that well-intended efforts could result in barriers to the conduct of research.

The Deans of New York's 14 medical schools have made clear our interest in working with any government body aiming to strengthen medical research with particular attention to the protection of the rights of anyone involved in these efforts. I hope

Subcommittee members and staff will feel free to call on me or Frank Jones, Executive Director of AMS, if any further information is needed or if we can serve as a resource to the Subcommittee.

Again, our thanks for the opportunity to submit this statement.

December 20, 1999

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Girl in crisis was guinea pig to docs

ALL Maria wanted last spring was a therapist to talk to about her depression.

Instead, she got bamboozled into an experiment.

"They put a clear cube around my head, tied around my neck," the 16-year-old Washington Heights girl, who didn't want her name published, said of her ordeal at the New York State Psychiatric Institute.

Then they pumped carbon dioxide into the cube.

Maria later wrote in a statement for an advocacy group:

"I had an oxygen tube in my nose ... The test was supposed to last for 40 minutes.

"I could only take it for 20 minutes ... I started to cry. A psychiatrist said to let me out. The person doing the test said to wait, but the psychiatrist said to quit.

"After the CO2 test, they said yes, I was depressed."

The test had nothing to do with depression — she was unwittingly used as a "control" in an experiment on panic disorders.

DOUGLAS MONTERO

The experiment Maria took part in was partially funded by the National Institute of Mental Health, which recently took a pretty remarkable step.

NIMH looked itself in mirror and said it didn't like what it saw.

It stopped recruiting new subjects in 29 of its 108 experiments.

Its researchers were asked to justify the "scientific value" of 50 other studies.

That took a lot of guts.

Gov. Pataki is probably scared to take the state Office of Mental Health — which runs state mental hospitals — and hold it up to the mirror.

But NIMH boss Dr. Steven Hyman, who is not running for president, isn't so squeamish.

He formed a new review panel to scrutinize "high risk" human experiments with no demonstrated benefits to patients.

The review will soon spread to institutes and schools that conduct experiments using NIMH money. State-run hospitals in the city — including the Washington Heights psychiatric institute Maria went to for help — get millions from the feds.

Meanwhile in Albany, a state task force recommended giving researchers the green light to conduct risky experiments on mental patients without their consent — even if there is no benefit to the patient.

The recommendations come several days after The Post reported on Joseph Santana, a 36-year-old mental patient who died after being given an experimental drug in a state-run hospital.

It comes several months after The Post reported on highly questionable fenfluramine experiments on healthy children in a state-run hospital.

Pataki and his press secretary, Zenia Mucha, aren't happy.

But neither is Maria, the naive Spanish kid from the Heights.

Maria wasn't physically hurt. But she felt used — and even more depressed.

Maria was referred to the psychiatric institute by a Columbia Presbyterian Medical Center doctor who had given her a physical. At the institute, a psychiatrist told her about the experiment that she thought would help her depression. She was offered $100 and not told the study was on panic disorder.

She didn't understand the consent form because it was full of medical jargon, but signed it anyway. Her mother can't read English that well and gave verbal consent over the telephone.

And the panic-inducing cube was only the first part of the test.

"They didn't [verbally] mention the tilt table." Maria wrote afterward.

Maria was strapped to a table that slowly elevates to a 60-degree angle. The table and Maria stayed tilted for 20 minutes.

"The child will be told that this is safe but may cause him or her to feel uncomfortable," the consent form describing the experiment says.

The doctor who recruited Maria, Dr. Donna L. Moreau, refused to comment about the experiment, which was performed on more than 120 other kids ages 7 to 18. Jack Gorman, the institute's deputy director, also refused to comment.

Federal documents show the study required "60 depressed, non-panic children" to serve as a control group.

Maria fit the bill, so instead of providing the girl help, they put her in an experiment — which may have stigmatized her and made her feel worse.

"They said it [the study] would help them to understand kids' depression," she wrote.

"I plan to ask them what was the benefit of the research to me — and what they plan to do with the research and the results of the tests they did to me."

Don't hold you breath, Maria. You were used.