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**Ethics of Research Involving Human Subjects: Development of
Policy in Response to the Public's Perceptions
George Washington University School of Public Health and
Health Services
October 21, 2008**

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JOSEF REUM, PH.D.: Welcome to our third year of public health ground rounds. We're very proud to host this series, which is sponsored by Pfizer and we wish to thank Pfizer and the Kaiser Family Foundation who will be web casting today's presentation and all of our grand rounds this year. If you missed last month's session with the director of the Center for Disease Control, please go to kaisernetwork.org to view that presentation.

You may have heard that in Washington there's a big conversation about transformational leaders and today I'm pleased to present to you someone who is a transformational leader in medicine, in public health, and in ethics.

We're pleased to welcome Dr. Robert Levine who will present "Ethics of Research Involving Human Subject: Development of Policy in Response to the Public's Perceptions." Dr. Levine received his medical degree from the George Washington University School of Medicine in 1958. He is now at Yale University, not a bad school, where he's the Professor of Medicine and Lecturer in Pharmacology and Senior Fellow in the Interdisciplinary Center for Bioethics.

Dr. Levine was the founding editor of IRB, a review of human subjects research and is the author of numerous publications including "Ethics and Regulation of Clinical

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Research." Dr. Levine has served as Chairperson of the Steering Committee for the Revision of the International Ethical Guidelines for Biomedical Research and in 2004; he received the outstanding achievement medal for the U.S. Department of Health and Human Services for his role in the development of the Belmont Report.

In 2008, he received the distinguished alumni scholar award from the George Washington University and he was one of the distinguished alums asked to present during the President's inauguration last year.

Bob Levine has transformed health care research not just in the United States but around the world and he continues to do so as a consultant for the CDC and he continues to do so as a consultant for all of us who hope to do good research with integrity. Please welcome Bob Levine [applause].

ROBERT J. LEVINE, M.D.: Thank you very much Dr. Reum for that very generous introduction. It's wonderful to be back in George Washington after all these many years. When I graduated from George Washington, the medical school was located in a small building near the corner of 13th and H Street. It had no elevator or it had one elevator, but the students were forbidden to use it [laughter] and each morning, we walked up five flights to the anatomy lab. You've come a long way [laughter]. The building's jave come a long way and

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the institution called George Washington University has also come a long way.

I've been out of touch for many years until about a year and a half ago when I received the award from the university that Dr. Reum mentioned. Ever since that time, now that I'm back in touch with the new George Washington, I've become almost a commuter visiting George Washington for all sorts of things, the most recent trip being my 50th reunion celebration, a wonderful event.

I'm going to talk to you this morning or this afternoon, this afternoon yes, about something that, over the last 20 or 30 years, has become central in my own research and education interests. On my flight down here, the pilot started the engine and said we've gotten a bad signal, there's something wrong with the airplane's engine but don't worry, it's a little sort of glitch that's like a home computer. If you turn it off and turn it on again, it might go away [laughter]. So he turned off the engine and then a little while later turned it back on and he said, yes, it went away. We're okay and proceeded [laughter] to take off.

I'm going to talk to you about the ethics of research involved in human subjects and I'm going to approach this topic from the point of view of reviewing the history of the field. Why review the history of the field today?

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Well first, I think the history is a marvelous story. It's fascinating but that's not a good enough excuse to get you all out here in the middle of the day. The more important reason is that as you review the regulations, the ethics of research involving human subjects, you will find a lot of sentences in the federal register or in international documents that don't seem particularly well connected.

Reviewing the history of the field lets you know what problems those who wrote these sentences had in mind. What did they think they were going to fix by writing these regulations? Secondly gives you an intellectual framework and what we'll see is that all of these seemingly disconnected sentences all hang together around a small number of central themes. With this intellectual framework, when you're doing research and you are trying to figure out what the right thing to do is, and the guidance you get from the regulations seems vague and it almost always does, knowing the intellectual framework will help you figure out what to do in particular cases.

I'm going to begin my story about 30 years ago or 34 years ago in 1974 when Congress passed the National Research Act. This act created the National Commission for the Protection of Subjects of Biomedical and Behavioral Research. In 1974, I could say that without taking a breath in the middle.

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This act assigned to this commission two major charges. The first was to identify the ethical principles, which should underlie the conduct of research. Now note that I've highlighted the word identify. It told this commission to identify principles. This reflects an assumption that they're already out there waiting to be identified. It didn't tell them to invent principles as national commissions so often do.

Secondly, it told this commission to make recommendations for guidelines for the protection of human research subjects. That's a fairly benign statement but it also said that these recommendations had to be converted in the regulations by the secretary of what was then called the Department of Health Education and Welfare.

They had to be converted within 180 days or else the secretary would have to publish good reasons why not to do so. That's quite a powerful charge given to a nongovernmental agency. Never before has Congress given a nongovernmental agency the authority to write regulations. I might also say it hasn't done so since then either but the fact that it did so on this occasion means that the regulations they recommended in the 1970s are the same or had the same themes, the same outlines as the regulations that we must follow to this day.

It identified, as it was charged, ethical principles. I know you've all seen these ethical principles but they come out

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in the literature under many different names. So I just wanted to put them up here in front of you so that we're all talking the same language.

They're listed in historical order. That is the order in which the commission identified them. Many people think that because they're listed in order that one has priority over another that you have to tend to respect per persons and when you're done with that, then you tend to beneficence. This is not at all correct. The National Commission tended that at least in the abstract that each of these commissions had equal moral weight.

Respect for persons, you sometimes read this called autonomy or respect for autonomy. It all means the same thing, beneficence, the requirement to do good, sometimes these days you read two separate principles, one called beneficence do good and one called non-maleficence, which means do no harm. The National Commission group these as part of the same principle and call it all beneficence.

Thirdly, the National Commission referred to a principle called justice. They called it simply justice when what it really meant was distributive justice. When there's not enough to go around, how do you decide who gets first shot at it, the mirror image of that distribution of burdens. It also

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identified, made recommendations for regulations. We call these norms or rules.

Now these are not like the principles. These do have an order, a hierarchy, a sequence. You've got to take care of the early ones before you can even look at the later ones. What I'm doing now is I'm going to group each of these norms under the principle that it's most closely related to.

The first of these is there must be good research design. Obviously if you don't have good research design, you're not going to produce any benefits for anyone. If your research design is no good, you simply shouldn't do it. It doesn't matter how good your consent forms are or how well you attended to the other ethical norms.

The second is that there must be competent investigators. Our reason for this is that kind of like with good research design, we believe that competent investigators are more likely to develop something useful than incompetent investigators but when you're dealing with research involving humans as subjects, an additional competence is required.

You must not only be a good researcher, you must have the necessary skills to monitor the wellbeing of the subjects to see if there's any evidence that one of them might get harmed and if so, you have to have what it takes to intervene, perhaps withdraw the subject from the research or perhaps

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administer corrective or anecdote to some other thing that can give him during the research.

Thirdly, there is a much more familiar requirement for a balance, a favorable or proportionate balance of risks and benefits. Under respect for persons, we have the requirement for informed consent and the requirements to respect people's privacy and maintain confidentiality of the private information that you take during the course of conducting research, private information about the research subject.

Finally, under justice, we have a requirement that there be equitable selection of research subjects. I'm going to have more to say about each of these norms as I go along but I just wanted to get them out there in front of you.

I also want to say at this point that given all the pages and pages of stuff in the Code of Federal regulations or the federal register, this is basically it. All of the substantive rules, found in all of those pages, are just variations on these six major themes. It'll tell you when you can get a document for informed consent and when you don't have to. It'll tell you specifically about how do you select subjects equitably but everything in there, all of the substantive normative requirements are basically variations of these six simple themes.

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There's plenty of procedural rules in the regulations but I can't organize them into any particularly interesting statement. You just have to follow the procedures but here are the substantive ethical rules.

Now as I mentioned, the commission was told to identify ethical principles with the assumption that they were out there waiting to be identified. The way the commission did this is to look back at past statements of research, ethics, and law to see if it could find any, at least implicit mention of anything that could be called an ethical principle.

The first place it looked was at the Nuremberg Code. That's because the Nuremberg Code was the first international document code of ethics for research on human subjects. This is a code that was developed in the city of Nuremberg in Germany shortly after the end of World War II. It was developed at a tribunal called the Nuremberg Tribunals.

There were several Nuremberg Tribunals. The one we're interested in today is called the Doctors' Trial where they put Nazi research physicians and their associates on trials, capital offenses. They were charged with capital offenses. The charge, the formal charge was crimes against humanity.

Many people think the Nuremberg Code was written to establish standards for that trial but that can't be in law, international and national. You can't try somebody for having

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violated a law that has not yet been written. The Nuremberg Code was meant to take the principles of international law and particularize them so that they applied to medical research with the expectation that in the future, research physicians would be held accountable for following these rules.

As they noted in the Nuremberg Code in the preamble, the research was done on quote, a social persons. They were prisoners in concentration camps, people that the Nazi regime had called, again I quote, life unworthy of life. These people were expected to die. There was no regard for their rights or for their welfare and if they didn't die during the research, they would be killed in other ways.

Early in the war, they were shot. Late in the war, they were killed in the much more efficient gas chambers. I visited the one in Auschwitz, which could kill 10,000 people at a time, which was operated on a twice-daily basis.

It's no wonder then that the Nuremberg Tribunal showed a special interest in their rights and in their wellbeing. The first statement in the Nuremberg Code is the voluntary consent of the human subjects is absolutely essential. In this, the National Commission found an implicit statement of the principle of respect for persons.

There are ten principles in the Nuremberg Code and I'm only going to mention three of the others because that's all I

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need to make my case. The experiment should yield results for the good of society avoiding all unnecessary suffering and injury and the risks should never exceed the humanitarian importance of the problem to be solved.

In these three statements, the Commission found the implicit statement of the principle of beneficence, which as I mentioned earlier, also includes nonmaleficence or do no harm in the way the National Commission developed these principles.

A closer look at the principle of respect for persons, the term respect for persons refers to a secular philosophical principle. It has its antecedents in Judao-Christian tradition, which teaches that all human beings have infinite value and that they are never to be used as means or instrumentalities for someone else's purposes. The way Immanuel Kant, a German philosopher writing in the 18th century, put it and so is to treat humanity in every case as an end and never merely as a means.

Now the National Commission Americanized this principle. I'll show you what I mean by that. it said that respect for persons incorporates at least two ethical convictions. First that individuals should be treated as autonomous agents. This focus on autonomy reflects an American perspective.

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In Western civilization generally, we place a high priority on the right of people to be free to choose what they're going to do but even within Western civilization, the priority that Americans place on the right to be self-determinant, stands out within Western civilization.

Now given that Western civilization is only about 20-percent of the world's population and the rest of the world places a much lower priority on liberty or autonomy or self-determination, it doesn't surprise me in the least that we have great problems working in Africa or in Asia convincing them that our way of getting informed consent and its documentation makes any sense. There's a lot of misunderstandings internationally about the requirement for informed consent and for consent forms.

What about beneficence? Beneficence has a very long tradition in medical ethics. When students first arrived to enroll in medical school, during the first week they generally have an orientation and during this orientation, some member of the faculty, preferably middle-aged or older, stands up and gives them a lecture on the Ethos of the medical profession.

Usually it said that the first principle of medical ethics is do no harm. Very often it's said in Latin, *primum non nocere*. I guess it's because in this country, if you say it in Latin, it has more moral clout [laughter]. If you translate

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this Latin statement literally, it means first or above all do no harm. We're told, we tell the medical students that this is the first principle because it's in the Oath of Hippocrates. Already we've told them two incorrect things.

First as we search the entire body of writings, what we call the Hippocratic corpus signed by Hippocrates over a period of 450 years. Thank you, I see some skeptical looks [laughter]. No, Hippocrates was not an immortal but in his time and around his time in Greece, if you were a physician and you wanted anybody else to read what you had written, you signed Hippocrates.

Now some of this stuff was actually written by the mortal who had the name Hippocrates but we're not confident which is which but as we review all of that, we only find one statement that comes close to do no harm and that's not in the oath. It's in a book called "Epidemics," which does not mean epidemics as we understand epidemiology in Greek it's "epi," upon, "demics," the population. It's more like sociology. The statement is about diseases, two things, to help or at least to do no harm.

Now for people who believe that ethics discussion begins with the tradition we've received historically and that if we ever want to change that, the burden of proof that we

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should change that rests with the person who would make such a change. I'm one such person. I believe that.

Then it's very comforting that we have not received the tradition that says above all do no harm. If that were the first principle, that would really have almost all therapeutics. Everything we do to patients, every time we give the patient a drug, we run the risk of doing some harm. Even aspirins can kill you.

So when they say about diseases, two things to help, or at least to do no harm, it's much more compatible with the modern notions of risk/benefit balancing than primum non nocere.

The National Commission said that beneficence consists of two general rules. One, do no harm but now didn't I just tell you that was not the first principle? Well what the commission means is not above all do no harm but never deliberately injure a human being no matter how important the knowledge is you're pursuing.

You can run a statistical risk of injury as long as you have persuaded an institutional review board that the risk is justified in terms of the benefit you expect or hope will come of it but you may not deliberately injure, say I'm going to cripple that person because I want to find a cure for something.

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Secondly, there is the exhortation to maximize possible benefits and minimize possible harms. Back to the Nuremberg Code for a minute, as far as I can tell, promulgation of the Nuremberg Code had no important effect on the conduct of research anywhere in the world. There's reasons for this.

First, physicians thought it was unrelated to the real world of biomedical research. It was full of abstractions and didn't take into account the existential experience of physicians as they were doing research.

Another reason is that it was classified as secret. The Nuremberg Tribunals were conducted under the auspices of the U.S. Department of the Army. It was their custom to classify any document they produced as secret. It doesn't mean you couldn't find out what was in it if you wanted to. In fact, it was published in the American Medical Association Journal. Let me tell you what I mean by this kind of secret from that of my own experience.

Around 1980 during the first Persian Gulf War, I was called by the Department of Defense asking if I would serve as an expert witness in litigation against the Department for using American troops in the Persian Gulf as research subjects without their informed consent.

I said well what are these drugs that you're using without informed consent. He said I can't tell you. They're

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classified as secret. I said would it be fair for me to assume that the three drugs I saw mentioned on the front page of the New York Times this morning [laughter] are the drugs that you're concerned about. He said yes, it would be fair to assume that but I'm not allowed to tell you [laughter].

There are higher levels of secret that nobody can get access to but at the lowest level, these secrets are pretty available. The point I'm trying to make though is that when an agency wants people to follow a code of ethics, it has symbolic significance that they have classified it as a secret document. It means that there seems to be a lack of enthusiasm about having people follow the rules set forth in the document.

Now in 1953 at the World Medical Association gave a charge to its medical ethics committee to write a code of ethics for physicians. On this occasion, in the memorandum establishing this project, it says that Nuremberg gives us no help. It simply sets the standards for criminal prosecution.

This just exemplifies the attitude of the medical profession worldwide toward the Nuremberg code. This does not mean that the Nuremberg Code is without influence.

When the World Medical Association's committee finally created the document that could be approved by the general assembly of the World Medical Association, it was 11 years later at their meeting in Helsinki, Finland. They called the

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document the Declaration of Helsinki. It's been amended several times since then in Edinburgh, Washington, Hong Kong, various other places but it retains the name Declaration of Helsinki.

What it does is interprets the principles we get from Nuremberg but interprets them in a way that makes them relevant to the empirical realities of medical research.

I'll give a couple of examples. In Article 1.11, it says in case of legal incompetence, informed consent should be obtained from the legal guardian or permission from the responsible relative. Now contrast that with Nuremberg's requirement. The voluntary consent of the human subject is absolutely essential.

The Tribunal was informed, at the time, by one of its American consultants, Leo Alexander, a psychiatrist from Boston, that if they said the consent of the subject was absolutely essential, that would rule out so much research designed to develop therapies for his patient population, people with cognitive disability.

The Tribunal responded, look the job of a Tribunal is to consider the case presented to it. We were not presented the case of attempting to develop new therapies for people, for any people much less people with cognitive disabilities. If you want a code of ethics governing that, you'll have to go out and develop your own code of ethics.

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Often people are trying to portray the Tribunal at Nuremberg as being stupid. They weren't stupid. They limited their charge to what they were told to do.

Another example, some risks are just to bide by potential therapeutic or diagnostic value for the patient. What a contrast that is to the Nuremberg standard that risks had to be justified in terms of the humanitarian importance of the knowledge to be gained.

It's clear to those who wrote Helsinki that in most research, the most serious risks come from the drugs, devices, vaccines that you're testing. In a clinical trial in the field of oncology, the drugs that are being tried can usually produce devastating loss of bone marrow of the mucosa of the gastrointestinal tract and so on.

These risks are justified in terms of the therapeutic potential for the patient. The risks that are truly due to research that are not justified in terms of hope for a patient benefit are really very trivial risks. In that same clinical trial, the procedures done for research purposes are randomization, perhaps getting more blood tests and other diagnostic tests to monitor the patient and the effect of the treatment. These usually present very little or what the regulations call minimal risk.

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So these are just two examples of the ways in which the Declaration of Helsinki interpreted the Nuremberg principles so that they would be meaningful in the specific context of medical research.

Now unlike Nuremberg, Helsinki had immediate effects. Almost overnight, the journals and the meetings of national and regional organizations said you must, if you submit a paper for publication, if you submit an abstract for presentation at our meeting, you must sign a statement that you have done the research in compliance with the requirements of the Declaration of Helsinki. Instant impact.

I was shortly thereafter editor of a journal called Clinical Research and participated in the development of these forums that said you followed the rules of Helsinki.

This also paved the way for the era of exposés. Before Helsinki, if you wanted to point at a research project and say that you thought it was unethical, you would have to say something like I think that research is unethical because it places the good of society before the interests of the individual patient.

Pretty tough to say if you're out there all alone trying to formulate a reason for why you think something's unethical but after Helsinki was published, you could say this research appears to violate principle 3.6 of the Declaration of

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Helsinki. It's the same thing. However, now the words have been put together for you and now instead of being out there all alone, you've got the weight of the World Medical Association standing behind your vision of what's ethical and what's not ethical.

The first great exposé in the United States was written by a man named Henry Beecher. Beecher was not an investigative journalist. Beecher was Chair of the Department of Anesthesiology at the Harvard Medical School, Chief of the Anesthesiology Department at the Massachusetts General Hospital, a most prestigious position.

He did his work giving general anesthesia in a room called the Ether Dome where many people think there was the first demonstration of the value of using general anesthesia to support surgery, at least people from the Northeast believe that. There are those from the Southeast who believe it was done in Alabama but that's an argument for another day, corporate [inaudible] followers.

Now Henry Beecher wrote or what he did is he reviewed major medical and scientific journals for the preceding five years and found in them 55 instances of what he called questionable ethics. This is 1965 so people did not use the same sort of language they use these days to make charges about ethics.

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He presented his paper with 55 cases to the editor of the New England Journal who did what editors do. He negotiated him down, 23 cases. So he wrote up his 23 cases and it was published in the New England Journal of Medicine. I can remember his publication. The impact of this publication was like a physical blow.

All this time we'd been allowed to believe that unethical research could only occur in a depraved regime like Nazi Germany and here we saw that it was being performed by the best and the brightest of American academic medicine.

Now following the etiquette at the times, no researcher was named. They didn't even name the journals in which the research was published but these were prominent researchers and prominent research findings. So all of us in academic medicine knew exactly who they were. In fact, at the time, one of them was negotiating with me to leave Yale to go to his medical school to head up the clinical pharmacology division.

Another guy that I had worked with at NIH subsequently became Chairman of Medicine at the hospital in which I interned at Peter Van Brigham Hospital. He was the only one that got cited as the principle investigator on two of these questionably ethical projects.

Now about a year later, the U.S. Surgeon General put out a memorandum saying that nobody could get money from the

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U.S. Public Health Service to do research unless he or she presented evidence of prior review of the judgment of the investigator by a committee of institutional associates.

This is the forerunner of the modern IRB, Institutional Review Board. The charge was to look after the rights and welfare of the subjects, to check out the methods of informed consent, and to reach an independent judgment about the risks and potential medical benefits. This is very close to what the central charge was to the IRBs are to this day.

A word about justice before I move into some more exposés. The commission didn't find any implicit statement of the principle of distributive justice anywhere in the earlier codes of ethics unless you count that statement in the preamble to Nuremberg about the social standing of the research subjects.

What the commission did is select it as its principle distributive justice, a requirement for fair sharing or equitable distribution of both burdens and benefits.

It came very close to endorsing the principles set out in a book, a major book of the 1970s called "A Theory of Justice," by John Rawls, a Professor at Harvard University.

Now whenever you set up a system for equitable distribution, you have to specify criteria that will be decisive in designing priorities to one or another to bear

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the benefits or the burdens. The criterion that the commission chose was vulnerability. This again echoes the criterion, the major criterion set forth in Rawls' book. That special consideration must be given to those who are vulnerable or disadvantaged.

Now we're pressed into thinking distributive justice when you're handing out benefits or good things. There's not enough to go around. How do you figure out who will have priority in getting them.

On the other side of it, there's distribution of burdens. We don't ordinarily think of distributive justice in distributing burdens. The best example of that that was prevalent in the 1960s and 70s was a selective service system where some people were going to be drafted into the Army or Navy and then sent somewhere to risk their lives perhaps in the service of the American values and so on.

What we're talking about here though is distribution of becoming a research subject. There was much concern at the time that certain vulnerable populations were selected more often because they couldn't protect their own interests, children, people who were institutionalized in mental institutions, and so on. The commission said no, there must be special protection of or such vulnerable or disadvantaged people.

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Exposés - I'm only going to mention a few. Tuskegee, who hasn't heard of Tuskegee? In the United States in the 21st century, the most powerful metaphor for evil in the name of research involving human subjects is Tuskegee. Until around 1990, the most powerful metaphor was Nazis. If you saw something that really looked bad, you'd say that reminds me of Nazi Germany and now this has been replaced by that reminds me of Tuskegee.

Marsha Angell, editor of the New England Journal of Medicine, writing about research being done in Africa in 1987, used the metaphor of this reminds me of Nazi research. Ten years later, writing to denounce the placebo controlled trials of the ACT in the prevention of perinatal transmission of AIDS, she said that reminds me of Tuskegee. It's the same charge using the metaphor of the decade.

At Tuskegee, 400 men with syphilis had treatment withheld. Why did they do this? They wanted to find out what untreated syphilis looked like. There was good reason to do this in 1932 when the research started. The treatments for syphilis were organic preparations of arsenic, bismuth, mercury, poisonous stuff. They didn't really know for sure which of the lesions of late tertiary syphilis were due to the bacteria in which were due to the treatment.

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Under the principle of maleficence, you might have been able to justify this research until around 1946 when penicillin became available for use in a civilian population. Now we knew we had something that we say, unless you were allergic an effect that was no justification for continuing this research further and yet it was continued until 1971 when it was exposed by an investigative journalist in the Washington Post.

What about the other ethical principles? Respect for persons? Well in 1932, nobody got consent from a patient to be a research subject. Somebody in a white coat walks up to a patient and says they want blood. The patient says well that's what people in white coats do and it's probably for my good but if you walk up to a normal person, what we call a healthy control or normal volunteer, I want your blood, that person's likely to say what for? Before you know it, you're telling your purpose, their risks. Before you know it, you're getting informed consent.

As a practical matter, consent for normal volunteers preceded consent for patients by about 60 years. it wasn't until the early 1960s that we began to routinely get consent from patients to participate in research.

So what's the big fuss at Tuskegee? These were patients. Well the tradition permitted not telling what you were doing. It did not permit telling lies. Many lies were told

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to these men. Yes you were going to have spinal taps from time to time and the purpose of these spinal taps is that it's a special new form of treatment. That wasn't true.

The purpose of the spinal taps was to follow the proteins in the spinal fluid to chart the progress of the disease. So this was a violation then of norms arising in the principle of respect for persons.

What about justice? The subjects of this research were Black men, most of them illiterate living in a rural county in Alabama. Given what racial prejudice looked like in the Southeastern United States in 1932, it's hard to imagine a more vulnerable adult free-living population. So for this reason, we say that we have a violation here of each of the three of norms arising in each of the three ethical principles.

I'm going to mention one other exposé in a little bit of detail and that's Willow Brook. This is where they fed mentally retarded children crude extracts of human stool with the aim of figuring out what was the mode of transmission of hepatitis and subsequently, what was the cause of the agents.

The research was very successful. It resulted in knowledge of what the transmission agent was. It resulted in the development of administering gamma globulin to mitigate the severity of disease after exposure and even contributed importantly to the development of vaccine in the 1970s.

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What was wrong with it? Well the subjects were mentally retarded kids, four or five years old. They were exposed to a dangerous virus, one that could cause a deadly disease. The parents were not entirely free to make choices.

They were told that there's a two-year waiting list to get your child into Willow Brook unless you're willing to put them in the research unit where upon we can find a bed probably later today or tomorrow.

In the view of most of my colleagues, this was grossly unethical research. So I was astonished in 1973 to read, in the New England Journal of Medicine, a follow-up report of the Willow Brook studies along with an editorial by the editor Franz Ingelfinger, saying it is the policy of this journal not to publish reports of research, which in the view of the editorial board, have been conducted unethically.

Therefore publication of the follow-up of Willow Brook in this issue of the journal can be taken to mean that in the view of the editorial board, this research was on balance, ethical.

Who's this guy Ingelfinger? Not only was he a distinguished researcher, a widely recognized expert of gastrointestinal disease but also he'd been recognized by the Hastings Center as the recipient of its Beecher Award, which

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meant the most distinguished contribution to the field of medical ethics over a lifetime.

This was not just some guy who didn't know anything about ethics that comes to this conclusion. I tell you this story because of the effect it had on me. It gave me a bit of humility that I'm not so quick to point at a research project and say that looks unethical until I've had an opportunity to review all of the details.

I reviewed all of the details of Willow Brook and decided I disagreed with Ingelfinger [laughter] but knowing him, he and I worked together and we even wrote a book together, knowing him as I did, it made me take his editorial very seriously.

Some other exposés, in the Jewish Chronic Disease Hospital, they injected live cancer cells intravenously in order to study the transplant rejection phenomenon. I could go into details of the other T-Room trade [misspelled?], obedience to authority are studies in sociology and psychology. I just wanted to let you know that physicians weren't the only troublemakers around.

Now this then brings me back to 1974. Now I hope you understand what in 1974 the Congress found it necessary to establish the National Commission. It was responding to exposés of this sort. What I'd like to do is to spend a few minutes

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reviewing the same time period showing you the reactions of the public.

Ever since day one, public policy in the field of human subjects research has reflected an attitude of protectionism. Subjects had to be protected from injury and from exploitation by the powerful socially and economically powerful scientists.

What we saw is in the United States the early policies were called policy for the protection of human research subjects and responsibility for monitoring compliance was given to an office for the protection from research risks.

In the 1960s, there were various statements that illustrated this attitude. In 1968, we saw the first national symposium on the ethics of research involving human subjects. It was held at Columbia University and resulted in a very famous book. The first lecture and then the first article in the book was by Hans Jonas, a celebrated philosopher in the field of ethics.

His essay is called "Reflections on Experimentation with Human Beings." He repeatedly referred to conscription of subjects to sacrifice themselves in the service of the collected. This is language lifted directly from writings about selective service, mandatory service in the Army or Navy.

Like those who were conscripted into the service, he said research subjects are conscripted to sacrifice themselves

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in the service of the collected like those who had been taken into the Army or Navy to go off to distant lands to expose themselves to the possibility of death or disability. This is the metaphor that Hans Jonas developed.

He wasn't making anything up. That's the way people thought about medical research in those days. Two years earlier, the United Nations General Assembly adopted the covenant on civil and political rights. This is Article seven. No one shall be subjected to torture or to cruel, inhuman, or degrading treatment or punishment. In particular no one should be subjected without his free consent to medical experimentation.

Look what they've done. They have essentially said that medical experimentation is a subset of a larger category called torture or cruel, inhuman, or degrading treatment or punishment. This is the attitude that informed thinking and policy making about research in the 1960s and 70s. I see that

I'm a little passed one and I'm told this ends at 1:30 but if I'm overstaying my welcome, let me know. I'm getting very close to the end and hope to have a few minutes for comments and questions.

This attitude about research remained in place. Several people wrote articles saying it's not all that dangerous to be a research subject. In my article on the topic, I said mostly

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what you're asking people to do is to urinate in a bottle instead of in the toilet. This had no effect on the policymaking scene.

The thing that turned policy around was the placebo-controlled trial of AZT in the treatment of AIDS in 1986. During this trial, a new voice was heard in the United States, the voice of what we came to call AIDS activists. These are extraordinarily well-informed, highly intelligent, invariably abrasive people who we usually write. Their voice became a very powerful voice in the health policy arena.

When I say abrasive, they refer to the Secretary of Health and Human Services as having hands stained with the blood of murdered African infants and things like that. They refer to the Director of the NIH as a murderer.

They said that we notice that people are referring to enrollment in this clinical trial as a great burden but it's no. Enrollment's a benefit. It's the only way that these men can get access to the only drug that anyone thinks is directed at the cause of the disease. It's only a 50-percent chance but if they don't enroll, there's no chance at all.

They also said that for these men, it is the only way they can get medical care. In the 1980s, insurance companies were trying to find ways to exclude people in the at-risk groups for AIDS. They were forbidden by regulations, in most

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places, to ask about sexual preference and other such things that might have put men in an at-risk group.

So some of the developed a policy that they would decline insurance for any single male living in a large city because the risk was just too high. The perception of benefit in this trial was so strong that the men with AIDS falsified inclusion criteria to get in. Usually this is, turns the whole perception of research as a burden inside out. The perception of benefit was so strong that their physicians cooperated in the falsification.

One of the entry criteria was that you had to produce biopsy evidence that you had recovered from a bout of pneumocystis carinii pneumonia. It's very hard to produce a biopsy report of that sort without the complicity of a physician and their physicians cooperated in producing these reports. Thinking back on it, it's a wonder that we learned anything from that trial.

Now the vision in 1980s then was formed in response to these considerations. We stopped talking about investigational new drugs as potential thalidomides and now we talked about them as promising new therapies.

We developed, the Food and Drug Administration helped us develop new categories of research called expanded access in parallel track where people were assured or certain types of

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people were assured access to investigational new drugs even at the beginning of phase II. That means even as you're beginning the very first human experiment to see whether or not these drugs had the effect that was intent they were sure to access to these drugs.

In phase I, all you do is develop information about toxicity. You don't begin to know whether or not the drug has any good effect. Participation in the clinical trial was seen as beneficial, giving access to investigational drugs, medical care, and even more importantly, benefits for the group.

On the occasion of 1986 and the next couple of years, we began thinking seriously about the fact that we had been protecting certain vulnerable populations from participating in research and what we had done is created a serious class injustice.

Children were kept out of clinical trials because they couldn't consent. The Professor, the Chair of Pediatrics from the University of Louisiana, wrote an article called "Therapeutic Orphans," in which he pointed out that since 1962 when we first had a requirement to demonstrate efficacy to get a new drug in the market place, only two drugs had been approved for use in children.

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All the rest of them had what he called orphaning clauses warning tests had not been done to support the recommendation of the use of this drug in children.

In the face of that, we turned the rules around so that today, there's a requirement that you include children, a requirement not only of health and human services but also of the Food and Drug Administration.

The same sort of argument went for the inclusion of women, ethnic and racial minorities. One woman in the late 80s put it well. She said just like children, we are also therapeutic orphans. We are being protected to death.

Part of her presentation showed that the same number of drugs had been approved for use in women as had been approved for use in children too since their requirement for demonstration of efficacy.

So now what we have is a regulatory system where most of the government says if you don't include children, women, minorities, we will give your research application a reduced priority score for funding.

This is not a matter of ethics say these agencies. This is a matter of science. You cannot be claiming to be pursuing generalizable knowledge when you develop exclusion criteria that keeps out more than 50-percent of human beings.

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In the case of FDA, they say the same thing about women and ethnic and racial minorities but about children, they say if you include children, there's not only a stick. There's a carrot. We will give you an extension of your exclusive rights to market for this drug, a six-month extension on your patent. For any drug that has a modest success in the market place, this is a tremendous amount of money.

I want to close by saying that the current vision that some people have that research is benign and beneficial is just as wrong as the earlier vision that it was all harmful and exploitative. I believe we must continue to encourage the conduct of good beneficial research while remaining vigilant to avoid abuses. Thank you very much [applause].

JOSEF REUM, PH.D.: Bob has agreed to take questions and our own Ethics Institute [inaudible] is here. So I'm going to turn to questions.

FEMALE SPEAKER: Hello Dr. Levine. I'm actually interested in what your views are on the recent cardiopulmonary study in infants, in newborn infants in the New England Journal of Medicine very recently that kind of pushes the definition of death that uses newborns to do it and that particularly study population, I thought that you might have some comments on.

ROBERT J. LEVINE, M.D.: Everyone know what we're talking about? Anyone not know? We're talking about a study

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where they got donors for heart transplants for infants not by following the usual brain death criteria where you have to show well all of the attributes of brain deaths and wait a certain period of time while maintaining all the other vegetative functions, the heart, the nutrition, the fluids, and so on.

Instead of that, they moved to cardiovascular death criteria where you can define death much earlier. There may be continuing evidence of brain function, electroencephalogram might show something and even if it didn't there, it might be brainstem activity.

The American definition of death, if I may get in a, a brain death, if I may get in an editorial comment, foolishly requires that the brain stem be dead as well in order to declare brain death.

This was published in the New England Journal. They had series of three patients who received transplants of hearts taken from infants who had died by cardiovascular criteria. They compared this with a group of what was it, 27 kids who got the ordinary transplant procedure and they found that this was good, effective, safe, and all that.

At issue in the commentary published in the same issue of the New England Journal is whether or not it was appropriate to bypass brain death criteria and move to cardiovascular death criteria.

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The entire argument was really not an exercise in research ethics. It was an exercise in brain death criteria. They couldn't find anybody to speak in favor of doing it this way. It was rightly pointed out that people, infants who die of, who are pronounced dead by cardiovascular criteria usually have irreversible loss of any function particularly cognitive function that could ever define them as regular human beings with cognitive capacity and so on and that they really were sacrificing very little.

The arguments were mainly over the principle of not following a rule that's become securely established in public policy without having the necessary high-level consultations resulting in the changes of the rules before going ahead with such behavior.

I will say that I understand what the pressures on these people are. It's very, very difficult to find hearts for infants. Many years ago, I was interviewed on what used to be called the McNeil-Lehrer Show, on the occasion of their having transplanted the heart from a baboon into a baby in California.

It was McNeil that was interviewing me. He said why is it so hard to find hearts for babies? I said well the usual donated heart is so big, it's from an adult that it won't fit into the baby's chest and do this work. He said well then why don't they use hearts from babies? I said well the way they

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find most heart donors is that after serious trauma or sudden disease insults, they look at their driver's license and it says donor on it. He said yes, what's the problem? I said well infants don't drive [laughter]. This is something that people reminded me about for a couple of years after that, the great knowledge that can be passed on by people in positions like mine [laughter]. Thank you.

JOSEF REUM, PH.D.: Any more questions?

MALE SPEAKER: Thank you for a lovely lecture.

[Inaudible] quick comment about on your stand about placebo-controlled infant trials, how you feel about that?

ROBERT J. LEVINE, M.D.: Oh my [laughter]. Have you read anything that I've written on the topic? Okay because that would be the subject of another lecture that would go over time for the hour.

The position reflected in Helsinki, until it was recently amended, was that placebo controls were unethical except in cases where there was no known standard therapy. I took the lead in arguing that Helsinki was wrong and had to be changed. The C-OPS [misspelled?] document that Dr. Reum referred to earlier where I chaired the steering committee for its development, developed a much more nuanced position on use of placebos.

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The interesting area is use of placebos in evaluating new drugs where there is already an existing treatment usually in a treatment where you think you can do better with your new drug. It's my position that if all you're dealing with is symptomatic relief, the placebo's okay.

If you're looking at a new drug for headaches, you can say to the patient we're going to give you either the new drug or a placebo and you have the right to withdraw at any time but if you withdraw, let us know why and in case it's because you can't stand your headache, we'll give you an effective drug.

In the treatment of diseases where under conditions of modern clinical trials, things could go wrong but never do like in the evaluation of new oral hypoglycemics, antihypertensive drugs given the usual way we run those clinical trials, things like that sort, I am in favor of placebo controls. Using active controls accomplishes nothing other than to make the trials very much less efficient and more expensive.

The third category begins to get a little bit more controversial and that's where you have a known effective drug but your new drug cannot be compared with the old drug because you would have a problem interpreting the results.

The prime example for this category would be the evaluation of atypical, antipsychotic drugs for the treatment of schizophrenia. There's reasons to believe that if you use

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active controls, you will end up with confusing results. That's one of the categories that would take about half of that hour I mentioned.

The final category where I would approve placebos is as in the cases, studies of perinatal transmission of HIV in low-resource countries where it's utterly noninteresting as to whether or not the standard use in the wealthy industrialized countries works. Even if you find that it does, they couldn't afford it. In such circumstances, I would, in a well-defined set of circumstances, I would approve the use of placebo or no treatment controls.

JOSEF REUM, PH.D.: Please join me in thanking Dr. Levine [applause].

[END RECORDING]