That medical research with human subjects presents ethical issues and problems is well known. I will talk about some of these in what follows. But it is worth emphasizing beforehand that if there is one overwhelming problem involving research that is of great of ethical importance, it is that there is not enough research. So the purpose of this presentation is not to point to ethical problems in research in order to discourage research. It is exactly the opposite: it is because of the importance of research that we want to make sure that our purpose is not blocked by ethical problems which we could have avoided if we thought about these things well before hand.

We value health research primarily because it offers relief from the burden of disease and disability. Moreover, science can be of great economic value, an engine for economic development.

A third reason to value health research is that it helps to ensure that the routine practice of medicine is effective and safe. Although health care is a scientific enterprise today, it remains true that most of what doctors learn, they learn from people who have done it in the past, who base their practices on what the people who taught them did. Most of what doctors do has never been shown to be safe or effective by experiments. We hope that most of what is safe and effective but some of it is not. Every year we find out that something that is customarily done all over the world is ineffective and sometimes we find out that these common practices are quite unsafe. Unless we do research, we will never find that out, which means that day in and day out, as patients go to doctors, the doctors give things to the patients that they believe will be beneficial but actually may be harmful. We need to go through everything that doctors do to make it all evidence based, and the only way to do this is through research.

Why should we be so concerned about the ethics of research? First of all, we all want to do the right thing and we have to figure out what the right thing is. If we don’t think about ethics and we start to go on our instincts, we allow our gut to tell us what the right choice is. Fortunately that works most of the time but sometimes it fails spectacularly.

Without the ability to trust each other and without the public’s ability to trust scientists there is no point in doing research.

* Transcript of the Inaugural Lecture at Universidad Centroamericana’s IV Interdisciplinary Research Congress, Managua, May 19th, 2010.
There is a second reason why ethics is important in research. We want people to trust scientists. For example, if someone is going to do research with human subjects, members of the public at some point have to agree to serve as participants. If the scientist is not trusted, there are no participants and the research cannot go forward. Furthermore, with no trust, the public is not going to support the use of government funds for the research either. So the public’s favorable perception of the ethics of the researcher is not just valuable, it’s essential if the research is going to be possible at all. Ethics is also essential if scientists are to trust each other. When a scientist sends an article to a journal, the journal does not ask for all the evidence that supports the results. Its editors assume that the scientist is not lying. The day that journals think they cannot trust scientists, is going to be a day in which science almost has to stop. The same holds for colleagues who read the journal articles and believe in the results and build on them in their own investigations. Without the ability to trust each other and without the public’s ability to trust scientists there is no point in doing research.

Trust has to be earned and can easily be lost. The way to earn it is to be vigilant about maintaining high ethical standards. One may think it is easy to know what is right and wrong. But there are many situations in which it is far from clear what the right thing to do would be. And the public has to not only believe that you are basically honest but that you have a good judgment too; that you have taken the time to think things through.

The single most important reason to talk about the ethics of research is that in the past some horribly unethical research has been done.

In what follows, I will speak first about the ethics of research with human subjects. In this area the problems are most acute for the obvious fact that they involve human beings, and what happens to human beings is always of ethical importance. I will talk a bit about the history of this subject and its current state today. After that, I will broaden the discussion to questions that transcend the subject.

Excuse me for dwelling for a few minutes on extremely unpleasant matters. But, the single most important reason to talk about the ethics of research is that in the past some horribly unethical research has been done. You may think those things cannot happen. But the historical record says those things have happened in the past so we need to think about it from time to time to make sure it does not happen again.

Health research began before World War II and accelerated tremendously in the 20th Century, especially just before and during the War. Many of the abuses that occurred had to do with national security. The very worst occurred in Nazi Germany, as all of you know, in the concentration camps. Fewer people may know that experiments that were equally barbarous were occurring on the other side of the world in Japanese occupied China. As the Cold War set in, some experiments both in the Soviet Union and in the United States—almost always kept very secret—were done that are rightly condemned today.

At the Nuremberg Doctors’ trial, some of the leading scientific researchers of the German regime were accused of having committed crimes against humanity. The most famous was racial biologist Dr. Josef Mengele. He sought out twins arriving at the death camps in cattle cars. In his experiments, one would be used as a control for the other. Few survived.
Other experiments were conducted in support of the war effort. The German air force was building airplanes that could go higher than any other airplanes had gone. That would expose the pilots to conditions of cold and oxygen deprivation. So they needed to know how cold a pilot could get before he blacked out. They took prisoners, froze them and made notes on when these people lost consciousness and when they died. They did the same thing with oxygen; they put prisoners in sealed tanks and slowly withdrew the oxygen until they died.

Half way around the world, Japanese biowarfare scientists carried out experiments that rivaled those of the Nazis in barbarity and number. Again, national security was believed to justify it all. For example, syphilis was a problem for the troops so they forced civilian women to have sex with infected soldiers to study the natural progression of the disease was at the level of the organs. Once a week they selected some of the women and carved them up so that they could see *in vivo* what was happening to the organs. After that they were killed. In other experiments, they studied frostbite by exposing adults and children to cold until their skin froze. All were subsequently killed The dead bodies froze and they piled them up outside their laboratory like logs. After a while the scientists referred to their human subjects as “logs”.

... unspeakable research continued in the post war era.

After the War the Nuremberg Tribunal issued a code of conduct for medical scientists that began with the statement that the consent of the individual is absolutely essential. Nevertheless some unspeakable research continued into the post war era. In the USSR, for example, the KGB sought a poison that would not turn up on an autopsy. Their scientists used political prisoners as guinea pigs in this effort. In the United States, military scientists sought to understand the effects of atomic radiation on civilian populations. In one institution for mentally retarded children, boys were told that they could enroll in something called the Science Club. Among its activities, it was later revealed, was the ingestion of breakfast cereal laced with radioactive isotopes. Neither the Soviet nor the American national security research seems to have been comparable to the Nazi and Japanese experiments, but their secrecy suggests that both governments knew that the research was unethical.

Not all of the regrettable research involved national security. In the history of medical experimentation in the United States, perhaps the most notorious abuse occurred in a study of the natural history of syphilis in African-American men. The research was based at the Tuskegee Institute, a medical research institute at a College specifically created for African Americans. The study began before the discovery of antibiotics, which offered the first real hope for arresting the course of the disease. But these men obtained no relief from this discovery. The scientific team never offered antibiotics to the participants and failed to inform them that a possible remedy had been invented. Indeed, the government scientists in charge of the research sent letters to hospitals and clinics in the area asking that the men not be offered antibiotics if they appeared for any reason seeking care. Many participants went to their grave without ever understanding that an inexpensive, plentiful drug that might have had a powerful therapeutic benefit was deliberately withheld from them.

One remarkable difference between the Tuskegee syphilis study and the others that I’ve mentioned was the lack of secrecy. The scientists published periodic progress reports in
reputable journals, none of which included discussions of the ethical issues involved (though we now know that the scientists were receiving strong protests in correspondence from scientific peers). Only when the story was told in a compelling way in a book written for the general public was the study shut down. In the end, the President of the United States offered the nation’s apology to the few surviving participants.

The landmark article for research ethics in the United States was written by Harvard’s professor Henry Beecher.

The landmark article for research ethics in the United States was written by Harvard’s professor Henry Beecher. It was published in the 1966 in the New England Journal of Medicine. Beecher noted ethical lapses in 22 experiments that were published in leading medical journals. This article provided documentary evidence that the mistreatment of human subjects in medical research was not limited to Nazis, and its publication had a profound effect on the regulation of medical research in the United States and, subsequently, abroad as well.

Although Beecher is now regarded in my field as a kind of patron saint, recent research provides hints that Beecher had once participated in clinical research that was insufficiently respectful of his patient-subjects. Beecher’s younger collaborator, Dr. Louis Lasagna, may have persuaded his mentor to reconsider the ethics of his research.

...if you want to do experiments on some people you cannot just go to the people and ask them, you have to show your plans to a committee specifically created to look at these plans to make sure that you are not planning to do anything unjustified.

After the publication of Beecher's article, things changed a lot. Within just a few years, country after country developed codes of conduct for researchers. Most important, they instituted prior review, a step that would earlier have been unthinkable. Prior review means that if you want to do experiments on some people you cannot just go to patients and ask them. You have to show your plans to a committee specifically created to look at these plans to make sure that you are not planning to do anything unjustified. If they find something that they do not like they insist that you change it and only after you get their approval are you allowed to approach the human subjects. Informed consent is something that happens after that. It is not a matter of people saying yes or no. It is unjustifiable to even ask people to say yes or no if you have violated some of the provisions of the ethics code.

Some scientists in the first generation of scientists who had to accept this requirement found the new requirements to be burdensome. The review committees were usually called Committees for the Protection of Human Subjects, but some scientists called them Committees for the Prevention of Research. Nevertheless, putting these Committees into place really marked a tremendous advance. Now it was essential that everybody who was involved in research think very hard about the ethical issues. If they did not, they were not allowed to do it. This has gone a long way now for over twenty years. These committees exist everywhere medical research is done in the United States. And because US regulations require that
all research conducted with public funds be reviewed by a Human Subjects Committee, these were created throughout the world at sites supported by US government funds. Many countries have acted independently to create their own ethical review mechanisms. Many agencies have initiated training programs in developing countries for members of these committees, and the World Health Organization has offered some support, including a recent casebook, available online without charge, on ethical issues in international health research.3

The Structure of Research Ethics

At the basis of the structure of research ethics are the ethical principles that we all live by. Although from one culture to another there is some variation, most of us agree on the basics. For example, no one thinks it is okay to kill someone to get their money; no one thinks it is okay to tell lies about someone in order to gain an advantage. These are common ethical beliefs that we all try to live by.

In the next level up in the hierarchy are general guidelines on the treatment of human subjects in research. The Nuremberg Tribunal’s Code of Ethics was issued in the late 1940s, and there have been many others since then. The best known is the Declaration of Helsinki, from the World Medical Association.

National regulations and oversight, the next level up in this diagram, do not exist in all countries. They are usually based on international guidelines but can be much more specific. For example, suppose you take somebody’s blood sample and tell them that you will use it for a diabetes experiment. If later you realize that you can use that same sample for a study of cancer, must you re-contact the subjects to ask their permission? Global guidelines do not say, and the
question is answered differently in different places. The final stage of ethical consideration in this structure is procedural: the Committee that you have to submit your plans to before you are allowed to approach human subjects and ask them to be in your study. Typically they are peers of the scientists, not bureaucrats. They are mostly scientist, but sometimes it is customary to add a few non-scientists to make sure you get a broad range of opinions. In general, they are educated and informed people who understand what is going on.

Why not just rely on the conscience of the investigator? This was the safeguard used in the past, and in fact Beecher himself believed that we should rely on educating scientists rather than prior review by ethics committees. One consideration in favor of committee review is the understandable tendency of investigators to harbor high hopes for success and value of their experiments – for if the research offers the next big hope for human kind, and that might justify some treatment of human subjects that otherwise would not be justified. But maybe they believe in this a little bit more than it is justified. More broadly, committees might be less prone to the common kinds of failures of ethical judgment to which we are all prone. Though no single member of the Committee is likely to avoid these lapses in judgment, we hope that by having several people involved their failings may cancel each other out and if the Committee as a whole reaches a consensus that what you want to do is justified, it should be okay. Generally this works pretty well. In the United States, these hopes are sometimes fulfilled and sometimes are not. Some Committees tend to intervene too much when not enough is at stake, and my own belief is that potentially valuable and justifiable research is not even submitted to committees for review because they fear Committee obstruction. Certainly there is a need to improve our system of ethical review, and many of us are working on this. Scientists believe that the committees will (mis-)use their authority, but in general the system works pretty well.

**These days, even in the United States, the issues that are most hotly debated have to do with research carried out not in the rich countries but in the poor ones.**

These days, even in the United States, the issues that are most hotly debated have to do with research carried out not in the rich countries but in the poor ones. Some of these debates have gone on now for many years and are nowhere near being resolved. The first one is whether or not, if you do an experiment with human subjects in a developing country, there is going to be the kind of ethical review which is now standard in most of the developed world. In some places there are such committees but there is no requirement of research to go through them. In Nigeria, for example, they have some committees and some of the people on the committees have undergone special training so they can run them well. But until recently it was up to the researcher to decide whether to submit their proposals to the committees. If they didn’t want to, they didn’t have to, and they can do the experiment anyway. As a result, researchers who might want to do something that would not meet commonly-accepted ethical standards would simply avoid prior review. And the committees would see only proposals likely to pass easily.

This leads us ask: Who is watching the committees? Is there any national oversight? Is there an agency of the government whose job it is to make sure the committees are working
well, and that everything is submitted to them, and that no experiments are allowed to go forward unless they receive the approval of these committees? The answer is usually not, in the poorest countries.

**Ethics committees have to be autonomous, they are making an ethical judgment and what they say has to be the last word.**

Then there is the question of the autonomy of these committees. This subject is problematic. Where are the ethics committees in an organization chart? Is there somebody above them who can overrule them? The fact is, they have to be autonomous if their existence is to be justified at all. They are making an ethical judgment and what they say has to be the last word. Often, research projects are of financial importance to the institution. And if the proposed research is unethical, then it should not be carried out; but a “no” from the committee might put an institution’s finances, including many jobs, at risk. Institutional officers, such as university chancellors and research directors, who bear responsibility for institutional financing and risk management, cannot be free to overrule an ethics committee. The result is either you have committees that are truly autonomous or you should not have them at all, and that is a very strange idea for a lot of people. This also leads to some problems, because that means if the committee makes a gross misjudgment there is nobody there who can correct them.

*...you can conduct a clinical trial in a developing country instead of doing it at home.*

“Outsourcing” is an extremely important word for clinical research in developing countries. In the rich countries it means that instead of relying on your own country to supply you with human subjects, you recruit people living in developing countries. There is a tremendous rush to do this. Why is this? It is widely suspected that people doing the trials do not want to have to put up with the ethical reviews. But sponsors of the trials insist that is not true. They say that when they go to a developing country they insist that the ethical standards be the same as they are at home because in the end they have to convince the regulatory authorities back home that the trial was done ethically or they cannot get approved for sale. The reason they say that they want to come to poor countries is that they get participants signed up really fast. And this is important because of the patent laws. For example, if they discover a molecule that might have a therapeutic effect and they have a limited number of years from the start of the filing of the patent to the expiration of the patent. Since that is when they make the money (profits drop sharply after patents expire), they need to recruit patients as fast as possible.

In New York, or London, recruitment may go for years before you have the right number, but if you go to South Africa you can get it in two days. Moreover, the people who sign up do it because they cannot afford care; they are pharmacologically naïve, which means there are not a lot of competing chemicals in the body. So these are much better subjects. So that is good for the companies. How about for local people? Is this a good thing or a bad thing? No one knows. In some cases it has been good for the development of the host site’s infrastructure because people are trained and sometimes the sponsors build laboratories and other health resources that otherwise would not have become available. And sometimes local sites can
get trial sponsors to contribute money for further training and for some patient care. But what effect it has on participant populations as a group we do not really know because no one has developed an adequate way to measure this. There is no doubt that the pace of outsourcing will increase. I don’t know whether there are such sites in Nicaragua; if not, you may hear from some of these sponsors in the future. Both host countries and sponsors’ countries ought to have better information on the net impact of these clinical trials on the enrolled patient population.

For the critics, what this amounts to is that developing countries of the world are saying to the drug companies of the developed world: “All we have is our people. Here, come take them”.

For the critics, what this amounts to is that developing countries of the world are saying to the drug companies of the developed world: “All we have is our people. Here, come take them”. They offer their bodies to the drug companies who then administer these medicines, find out what they need to know, go home and then sell products that people in the developing country can’t afford anyway. So this debate is still ongoing.

... a question about research in developing countries is control of the agenda.

And finally, a question about research in developing countries is control of the agenda. By agenda I mean, who decides what research should be done. For example, there was a study in Thailand that was aimed at coming up with a vaccine that would offer short-term protection against infectious disease. People in Thailand didn’t need short-term protection, they needed life-time protection. So, who was interested in short-term protection? It could be the military to send in soldiers for a limited tour of duty, or it could be drug companies that want to sell drugs to travelers. So this was done in Thailand and one of the leaders of drug control in Thailand thought that this was contrary to the priorities of Thailand. He said if he became the head of the drug control agency he would not allow more trials of this kind. So in Thailand they made strong efforts to control the agenda.

Unfortunately, disputes about conflicts of interest are now rife, they are commonplace, they are ubiquitous, we see them everywhere in scientific life, especially in the health field, but also in others.

So far all the questions have been about the treatment of human beings who engage as subjects of research. Now I am going to move to a much wider set of questions.

My final topic is the ethics of trust. Consider a routine visit of a patient to a doctor that results in a prescription for a drug. The patient’s subsequent purchase of the drug is ordinarily not based on the patient’s own assessment of its value or appropriateness to the patient’s health problem. The patient relies on the doctor’s expertise. Unless the doctor is a sub-specialist, he or she will in turn rely on the expertise of leading medical scientists who have conducted research on the drug or who have commended its use. Ideally, well-designed research studies provide an evidence base upon which influential practitioners reach sound and objective
judgments. But suppose that a drug company found a way to influence these practitioners and opinion leaders with money rather than with evidence. They could easily calculate what their return on investment would be if they funneled money to these people to increase sales. If profits would increase, they would (and do) have an incentive to act accordingly – if ethics doesn’t get in the way. When the scientific evidence does not support a doctor’s recommendations, these investments may be the only way to avoid a loss on the product.

Most of the leading researchers, the people who are most respected now, have very tight and extensive monetary involvement with the private industry.

Drug companies and other medical supply firms have found many ways to put money in the pockets of those who influence the prescribing habits of medical practitioners. They all create conflicts of interest. Unfortunately, conflicts of interest are now ubiquitous. We see them everywhere in scientific life, especially in the health field. Most of the leading researchers, the people who are most respected now, have very tight and extensive monetary involvement with the private industry. It is hard for the government to get advisors – on whether they rely for advice on whether to approve drugs – who do not have these financial ties. The most they can do is to say “well, you have all these ties, we want you to disclose them”. So before the Food and Drug Administration will have a meeting, they will list all the investments, and directorships, and paid lectureships, and all these things that their advisors have been treated to by the drug companies. There is a debate over whether disclosing does any good at all. At Harvard Medical School a number of well known medical researchers on the Faculty own part of these companies or receive large amounts of money from them or often give lectures at conventions in exchange for fees from these companies. The same is true of virtually all leading American medical research institutions.

We know that the goal of health research is health. And the goal of commerce, generally and at least partially, is to make money. What we don’t want is to have people who are doing health research that deviate from the health goal.

This is a very big problem. The essence is very obvious. We know that the goal of health research is health. And the goal of commerce, generally and at least partially, is to make money. It’s fine for people to make money by conducting research that will improve health. What we want to avoid is for the prospect of financial gain to tempt scientists or practitioners to deviate from sound science. The result would be health care that would be ineffective, inefficient, or even unsafe. Does this happen? There is little doubt that money is changing hands as drug firms seek influence over those who prescribe drugs; and those who carry out research are often benefitting financially as well. Whether these payments are resulting in unjustifiable research practices and medical practice is hotly debated. Although the public seems to be aware there is an issue, almost always the vast majority of people who are polled say “I trust my doctor completely”. And that’s understandable: we all feel a need to trust our doctors. We put our lives in their hands, and we will be reluctant to do so if we harbor serious doubts that our doctors will give higher priority to our health and safety than to how they can maximize rewards from drug companies for prescribing products that may not be
good for us. But if public trust is maintained in the face of growing evidence that the trust is undeserved, there could eventually be a catastrophic collapse. If you think this cannot happen, it just did. It did not happen in health care, it happened in the area of finance.

We are all living with the consequences of the financial crisis of the past two years. Trillions of dollars have been lost and many millions worldwide have lost the work that kept them and their families from poverty. To a large extent, this was the result of a collapse of trust following a long and deep erosion of ethical standards in American financial firms. People who couldn’t possibly pay back the money they owed on houses were nevertheless loaned money to buy those houses. The firms that gave them the money knew that they could never pay those loans. They didn’t care because they sold the indebtedness to other investors and would not be burdened by any eventual forfeiture. The investors, in turn, bought these financial instruments in large part because the bond ratings firms upon which the market relies to estimate risks changed their business practices so that they earned money from sellers of bonds rather than from buyers. They overlooked glaring defects in the bonds in order to keep their patronage and fees. Bonds that have proven to be worth nothing were awarded the highest possible ratings for safety. They were manufactured out of promises to repay loans that were made by people who couldn’t possibly repay those loans, and those who created and sold the bonds, and those who rated them, refrained from insisting on credible evidence of the debtors’ ability to pay. For a while, the system spread rewards as lenders pocketed commissions, rating agencies received their fees, and people who could not realistically expect to own houses were given home loans. But there were scholars and financial officers who knew this was all impossible. The math did not work out. The good times could continue only as long as investors were fooled. Eventually it all blew up catastrophically. Bankers did not trust other bankers, buyers didn’t trust sellers, no one trusted anybody; and without trust the financial system cannot work. Without extraordinary intervention by central banks we would have been thrown into a second Great Depression; even so, financial devastation is spreading globally and we don’t know when we are going to get past this.

We can all tell ourselves that even if we had the financial motives to do what we shouldn’t do, we wouldn’t be influenced by that.

So if you want to know if ethics is important, just look around you. The effects of ethical failure are obvious now. But until the crisis, only a small minority was appropriately skeptical of the false prosperity. Consider conflict of interest. It often does not seem unethical to the person who is involved in the conflict. Conflict of interest means that you have a financial motive to do something you should not do. We can all tell ourselves that even if we had the financial motives to do what we shouldn’t do, we wouldn’t be influenced by that. And when polls are done and people are asked if they think that they would do something they shouldn’t do because of money that is available for doing it, most people say no. But when they are asked “How about the people you work with?” they say “Oh, yes”. The math doesn’t hold up there either. If everybody thinks that all their neighbors give in to these influences and that they don’t, and all the neighbors think that they do, probably everybody is influenced. It is so very easy to deceive ourselves.
Those who become accustomed to placing themselves in conflicts of interest can easily convince themselves that they are acting honorably. If they look to the left and they look to the right find that they are acting no worse than their peers they may conclude –erroneously of course– that they are above reproach. As ethical standards deteriorate further, it will usually be possible to identify others who are acting worse and who make you look good by comparison. Self-deception comes easily, but after a while it is not enough to just be self deceptive. You have to actively deceive others. They have started to find that out in the financial area.

So we have learned from the financial crisis that a lack of ethics is catastrophically damaging.

We have learned from the financial crisis that a lack of ethics can be catastrophically damaging. If we’d had stronger ethics we wouldn’t be in the financial mess that we now find ourselves in.

The same may prove to be true in health research and medical practice. Thus far, scientists generally trust each other, patients tend to trust their doctors, and this trust makes the whole thing work. Take that away and we will be in big trouble. Perhaps we are approaching the tipping point, risking a catastrophic loss of trust on the part of patients and scientific peers. Should that happen we would realize that we should have put much more emphasis on ethics. There is no way to know how far we may be from this threshold. Some will demand proof that we are in acute risk before they agree to reduce conflicts of interest and outright deceptions that now seem to threaten the ethical integrity of medical research and practice. We cannot provide such proof. But if the ethical lapses in health care and health research lead to the same kinds of consequences produced by ethical lapses in the financial industry, we will regret that we ignored so many flashing warning signs.
Notas

1. An earlier study in Norway had focused on whites.
3. [http://extranet.who.int/iris/bitstream/123456789/984/1/9789241547727_eng.pdf](http://extranet.who.int/iris/bitstream/123456789/984/1/9789241547727_eng.pdf)