Protecting Human Subjects in Research — Occasional Views along a Road Less Traveled

by Greg Koski

Public trust in biomedical research is eroding rapidly because too many investigators participating in human subjects research have failed to take personal responsibility for their actions. In this essay, taken partly from an address to the 66th Annual Research Colloquium of the Massachusetts General Hospital, January 2001, and a presentation to the research community of the Washington University School of Medicine in September, 2000, in St. Louis, Missouri; Greg Koski shares his views about protecting human subjects in biomedical research.

At first they said it was a stroke. She was only about 60 years old. We had noticed a slight droop at the corner of her mouth for a couple of weeks, but didn't think much about it. An angiogram confirmed the diagnosis – there were no CT scans or MRIs in 1962. Glioblastoma multiforme, the doctors called it. We just called it a brain tumor.

My grandmother had always been a strong, active woman. Watching her cancer progress wasn't easy. First it took her personality, and then her ability to speak and stand. We watched the tumor take her pride, my family's life savings, and, finally, her life. But there was a bright spot during that year and a half between the resection and the recurrence. They called it *experimental treatment*. It involved a series of Co60 radiation exposures. No one knew whether or not it would work. It was just an experiment.

At the mention of the word "experiment" my ears perked up, as did my parents. It was as though someone had turned on a bright light in the darkness. Suddenly it seemed that we had an option where before we didn't. There was a hope that my grandmother *could* actually get better. And she did, for a while. Not long enough for us, but long enough for her to reclaim her dignity and say goodbye.

Even today, I am struck by the way my family reacted to the word "experiment." The prospect of participating in research truly offered my grandmother hope, and justified or not, we all believed that science would deliver a miracle. We trusted the doctors, even though they were doing experiments on my grandmother, because we believed they were trying to help her. And as far as I knew, everyone felt the same way.

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Being only twelve years old at the time, I didn't pay much attention to congressional hearings. My parents also had their own problems to deal with, and while they were probably appalled by the horrible birth defects that had been caused by thalidomide, they probably didn't note the passage of the Kefauver-Harris amendments, or the growing public concern about the safety of medical devices and drugs and the ways in which they were tested before being brought to market.

They certainly didn't know about the experiments that were going on in the laboratories of the department of anesthesia at the Massachusetts General Hospital. These experiments were probably classified anyway. The goal was to better understand the effects of drugs on the human thought process. At least that's the way the story was recounted to me by Louis Lasagna (personal account). Lou was a research fellow, working at the time with Professor Henry Beecher, the first chair of the department. Their volunteers came to the laboratory and signed a waiver before they took the study drugs. But Lou wasn't entirely comfortable with this arrangement and expressed his concerns to Dr. Henry Beecher. Apparently, Dr. Beecher wasn't comfortable with the arrangement either.

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Of course this study was before the 1966 paper in the *New England Journal of Medicine* in which Beecher alerted the American academic community to the fact that some human subjects were being exposed, without their knowledge and consent, to potentially dangerous research procedures and unproven "therapies," and that effective treatments were being withheld in the name of research (Beecher 1966). It was also before the revelations of the U.S. Public Health Service syphilis study. It was a different time.

But none of that mattered to me. I was going to be a doctor and a scientist, and one day, I would do something that would help people, something that would make their lives better. I got an early start. I was fourteen years old when I built a sleep laboratory in my basement. As the present day father of a budding young scientist, I can only imagine what must have gone through my father's mind when I asked him if he could get me an electroencephalograph, and I'm still more amazed that he did!

That summer, in 1964, I did my first human studies, subjecting ten of my friends to a series of nocturnal EEG recording sessions with multiple awakenings during the night to see what mental activity they recalled during various stages of sleep. I suppose that today we would call those "minimal risk" studies. Still, no one had reviewed them, no one had checked the safety of my laboratory, there was no mechanism for adverse event reporting. One could hardly have said that I had obtained informed consent. Nor would anyone have considered me qualified as a clinical investigator. I went ahead with the research anyway.

Ironically, at about the same time that I was presenting the results of my first human studies at the Fourth International Science Fair in St. Louis, the *New England Journal of Medicine* was publishing Henry Beecher's paper, "Ethics and Clinical Research." I didn't read that paper until 1989, when I was asked to serve on the Subcommittee on Human Studies, the institutional review board (IRB), at the Massachusetts General Hospital (MGH). I wished that I had read it earlier, because as I thought back to my science fair project, I realized that Beecher could been writing about me — a teenage Dr. Frankenstein of sorts.

The Beecher Paper — 35 Years Later

Thirty-five years have elapsed since my initial adventure in human studies, and twelve since I read that first article. A few weeks ago, while preparing this paper, I came across another of Beecher's works:

> What are the permissible limits to and the proper conditions for experimentation on human beings? . . . There can be no question that the exposure of human experimental subjects to test situations can involve risk of injury even in some necessary procedures....

> Granted that all reasonable precautions have been taken to protect the subjects from physical damage and the investigator from unethical practices, the possibility for injury may still remain. . . .
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> One must never minimize the importance of striving for true informed consent, but the patients greater safeguard in experimentation as in therapy is the skillful, informed, intelligent, honest, responsible, compassionate physician. . . . One hopes and believes these are in the majority. . . .
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> There is great need for constant reexamination of the ethical aspects of the procedures involved this need is imposed by progress in science and by the advances in moral and ethical standards. . . .
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> Wherever there are major concentrations of power, moral questions arise. . . . This is as true of the power of knowledge as it is of other forms of power. . . The extraordinary advances in medical knowledge are a case in point, for these can lead to the power to control, to manipulate, to alter human life as well as to cure human disease. . . . Security rests with the responsible investigator, who will refer difficult decisions to his peers. . . .
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> Morally responsible action is the result of making the best choice among several possibilities. . . . One irresponsible investigator can do great harm, not only to himself, to his subject, to his project, and to his institution, but also to the area of medical experimentation and, indeed, to the entire field of medicine. . . .

These words, taken from Beecher's *Research and the Individual: Human Studies*, are every bit as true and relevant today as they were three decades ago. As I read them for the first time both the language and its message resonated with me – surely I had read them before. But I had not. They were familiar to me because they so closely mirrored the message that I have been trying to deliver in the many presentations (some would call them sermons) that I have given across the country since becoming director of the Office for Human Research Protections (OHRP) in September 2000.

The uncanny similarity between Beecher's message and my own was first brought to my attention last fall by Tom Murray, the director of the Hastings Center for Bioethics, shortly after I had given the Fellows a presentation about the new direction of OHRP. As we were looking at the photos of Beecher, Hans Jonas, and other recipients of the Center's lifetime achievement award, he suggested that perhaps I had spent so much time at Massachusetts General Hospital that I had been possessed by the spirit of Henry Beecher!

While not being given to a belief in ghosts, I cannot deny that my years of service on the Subcommittee on Human Studies at the Massachusetts General Hospital — a committee originally chaired by Beecher himself— had an important impact on my development in this area. This subcommittee is charged with review and approval of all human research activities at the hospital. It was brought together long before there was a federal law requiring IRBs. At my first meeting of the subcommittee, a senior reviewer tossed a protocol on the table after completing his review, stating simply "this is something that might be done in a concentration camp, but not at Mass General." It was during those meetings that I had my first lessons in bioethics and my first real exposure to the protection of human subjects. They were, in fact, lessons handed down from Henry Beecher, whose code of

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ethics had strongly influenced the formulation of the hospital's Guiding Principles for Human Studies.

The lessons were as powerful as they were permanent. During my decade of experiences in human studies at Mass General, I came to realize that many others have been strongly influenced by the teachings of Henry Beecher, and that his spirit does indeed live on. Beecher was a giant among scholars, as courageous and committed as he was controversial. His 1966 paper stirred strong emotions among members of the academic community, and in many cases, engendered great resentment of him personally and vehement opposition to his views.

The Chilling Effect of Bad Research

Today we find ourselves in a situation not unlike that of thirty years ago, due at least in part to the tragic death of Jesse Gelsinger in a gene-transfer study in the fall of 1999. Although this was a sentinel event, since the 1960s we have witnessed a series of events that have gradually begun to erode confidence in the trust that the American people have traditionally held for biomedical science. For more than half a century, our society and our government have had to promulgate increasingly more stringent rules and regulations for the protection of human subjects in research in response to one abuse after another, often committed by the very same government that was charged with protecting the subjects of that research.

We have come to the point of needing a major crackdown on rogue investigators, institutions, and sponsors who stand accused of using research subjects in an unjust manner — solely as a means to an end, and in a disrespectful and sometimes harmful way. The public is calling for investigators to face serious civil penalties if they willfully neglect their responsibilities to protect their research subjects, and proposals for a new federal agency to police human research activities have been offered in Congress. Members of the public are increasingly skeptical and distrustful of research, and some are calling for severely limiting research activities.

How could we have come so far down this dangerous road? My own view is that for too long, some of us who engage in human research have failed to accept personal responsibility for our actions, and have failed to care enough about research subjects to put their interests ahead of our own. Too often we have placed our scientific, personal, and financial interests ahead of those of our research subjects. We've looked for an easier way for the science to be done, too often regarding the system for human subjects protection as nothing more than an obstacle to our research. Every time we do so, and every time a problem arises, as it inevitably does, the foundation of trust upon which human research depends is further weakened.

This erosion of trust is like the hole in the ozone layer of the atmosphere – if we don't change our ways, it will keep getting worse. If we don't stop the damage, we could destroy public faith in biomedical science to such an extent that there will be no willing participants for our research. We must work toward building a new culture in human research, one that truly embraces, rather than merely tolerates, consideration of the interests of research subjects. Respect for their interests must become the very foundation of responsible conduct in human research.

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A New Paradigm

Doing so requires that we adopt a new paradigm for human research protection. Beecher left us with a paradox. He believed that true informed consent was impossible to attain, and so the only real protection for research subjects rested in the investigator. While he saw the investigator as the individual best able to protect the interests of the subject, the investigator was at the same time the individual most likely to inflict harm, and most subject to conflicted interests.

Paradoxes frequently stem from the way we perceive a given situation. Our thinking is constrained by what we believe to be true. When we believed that the earth was the center the universe, we could not understand or explain the physical world. We now know that the earth is not the center of the universe. We have accepted a new paradigm, and we can now see things differently.

Beecher saw clinical research as the interaction between two principal parties, the patient/subject and the physician/investigator. Many ethicists, including Jay Katz, have noted that this too-limited view poses not only a paradox, but also an ethical dilemma. This paradox can be largely resolved by adopting a new paradigm, one which places concern for the well-being of our research subjects at the center of our attention and which recognizes that all of us who participate in this endeavor have shared goals and responsibilities.

Now is the time for definitive action. Indeed, many would say that the time is overdue. Everyone engaged in biomedical research must recognize that protecting the interests of research subjects is a primary goal, not an administrative hurdle that slows the research process. And as we face the challenge of moving to this new paradigm, we should also recognize that we have a remarkable opportunity. We have an opportunity to develop a new approach, one that has as its goal not just compliance with minimal regulatory requirements, but truly responsible conduct that establishes as a first priority the protection of human subjects as part of a system that recognizes and rewards responsible conduct. At the same time, we should work toward a system that is simpler, more uniform, and more efficient — as well as more effective. We have an opportunity to create a system that is less confrontational and more collaborative. We must now take advantage of these opportunities and work together toward these goals.

Working toward Professionalism in Human Subject Research

In many ways, the state of human research today resembles the state of medicine itself in the days before the Flexner report (Flexner 1910). At the turn-of-the-century, medical training involved largely an apprenticeship. There was little in the way of a formal curriculum, and no specific licensing requirements for entering the profession. The Flexner report led to the professionalization of medicine: the establishment of standards for performance and education that significantly improve the field of medicine. As we enter a new generation of human research, one that uses new tools, asks new questions, and raises prospects for encountering important new risks, we must be confident that we are properly prepared to meet these challenges.

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To do so, we must work toward the professionalization of human research. We must establish standards for education and training of all individuals participating in the research process, and move toward certification of their competency, whether they are investigators, research coordinators, IRB managers, or institutional officials. Individual participants must understand what his or her responsibilities are, and must make a commitment to fulfill them. We should develop standards for the accreditation of human subjects protection programs, standards that are based on performance and effectiveness of process, rather than on compliance with regulatory requirements as an end in itself.

These steps, in concert with meaningful assurances from academic institutions and other entities that engage in human studies, will help to ensure that the research is done properly, or not all.

By taking these steps in the private sector, rather than the government, we can achieve a higher standard of performance without the need for more numerous and restrictive regulations. We can allow greater flexibility, knowing that there will be greater accountability, and come closer to our true goals — doing high quality research that will benefit all of us without ever harming anyone.

We must also move to eliminate wherever possible conflicts of interest that may undermine confidence in our system, conflicts that can also undermine the integrity of science itself. As Henry Beecher said, "the American public has an intense interest in and considerable understanding – or at least awareness – of medical research. Research is increasing in geometric progression, supported by both financial and cultural factors in our society." We need to be certain that the pressures to do research do not once again drive us down the wrong road. We cannot allow financial or personal considerations that pose conflicting interests to undermine either the integrity of our science or the well-being of our subjects.

The American people harbor a great reservoir of hope and faith in science. We look to science and biomedical research to provide healthier lives and new cures for disease. We must work to make the public our partners in science and to better inform the public about the research process. Let us all continue to work together toward not only preserving, but also, actually building those reserves.

Conclusion

I never intended to be the director of the Office for Human Research Protections. I never even intended to serve on an IRB. There are times in our lives when, as Robert Frost wrote, "two roads diverge in the woods." We cannot know what lies ahead when we embark upon a new course, but there can be little doubt that the road less traveled is likely to offer up a journey that will be exciting and will likely offer up more challenges to those who choose to follow it in preference to a traditional path.

My personal choices have taken me in directions that I had not anticipated, and I am not sorry. Indeed, I believe that our efforts to build a new, more effective, and more efficient system for conducting and overseeing human research will succeed. While they may take us down a road less traveled, none of us will be traveling alone, and when we complete our journey, we will be able to look out with pride from a new vantage point, one that encompasses a new generation of research progress and hope for all.

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