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HUMAN RIGHTS AND HUMAN EXPERIMENTATION

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I feel privileged to have been asked to give this year's Weise lecture, to return to the school from which I graduated 45 years ago and to the hospital, then called the Peter Bent Brigham Hospital, where I spent the last three months of my student life. Fifteen years later, in 1964, I began my work on human experimentation, at a time when the discipline of bioethics did not exist. In those days only Henry Beecher and a handful of others thought seriously about the ethical problems raised by human experimentation. After eight years of sustained work, I turned to other scholarly pursuits and only recently returned to this field.

Ken Ryan asked me to speak about my past and present work, currently being enriched by serving on the President's Advisory Committee on Human Radiation Experiments. Its charge is to tell the story of, and to explicate the lessons to be learned from, the human experiments conducted by governmental agencies in collaboration with the medical profession during the 1940's through the 1970's. In reflecting about how to convey to you my concerns about human research, I thought that I could best do so if I were to speak first about my education as a physician and then about my experiences in the world of law.

I have remained a physician, I did not become a lawyer. I am also a teacher who has been fortunate to work in a setting surrounded by great students, where I have had the leisure to study and reflect about the tensions inherent in caring both for patients and research, in deferring both to physician authority and to patient autonomy, and in respecting the values transmitted to us both by our Hippocratic elders and by the framers of our Constitution.

I received a wonderful education at Harvard Medical School. What I learned then made me the physician I am today and, indeed, laid the foundation for my subsequent scholarly pursuits. Above all, I was taught to care for the patients who placed their trust in me, to listen to their complaints, to take meticulous histories, to arrive at a diagnosis only after having carefully considered all the alternatives and the available treatment modalities that might reduce their suffering. In my days at Harvard we were assigned few patients, worked in small groups with experienced clinicians whose attentiveness to the patients before them and us became indelibly imprinted in my professional psyche.

Yet, and this I realized decades later, I was only instructed to take patients into my caring custody by virtue of the authority that would be conferred on me as a physician once I had acquired the necessary expertise and clinical judgment. Sharing the burdens of decision with my patients by conversing with them about the decisions to be made with,

rather than for, them was not part of my training. The idea that patients may also be entitled to liberty was then part neither of the ethos of medicine nor of my education.

1945-1949 were exciting years for medical students at Harvard. Sidney Farber had just begun his pioneering work on the treatment of childhood leukemia, Robert Gross on the surgical treatment of congenital abnormalities of the heart, and Dwight Harken on the surgical treatment of mitral stenosis. Harken's remarkable contributions to the surgical treatment of mitral stenosis take me back to my days at the Brigham. I was puzzled then, though I did not give it much thought, that some interns and residents tried to keep certain patients out of Harken's sight because they knew that many might not survive surgery which he surely would recommend. In early 1949, Harken himself became depressed about his results and was almost ready to give up. Six of his first nine patients had died during or shortly after valvulotome surgery. But he decided to persevere for a while longer and once he modified his technique, adopting a procedure pioneered by the English surgeon Souttar in 1925, he succeeded. Then he could triumphantly and proudly announce that "[t]he question whether or not operations for patients with symptomatic mitral stenosis are worthwhile has now become academic." I do not know what Harken told his first nine patients but I did observe that caring young physicians kept patients from talking with him about whether or not to submit to surgery,

either not believing that Harken would level with them or not believing that patients could arrive at their own considered decisions about the advisability of surgery. Hiding patients from making such fateful choices seemed the only alternative.

I remember Conrad Wesselhoeft who gave us the one and only lecture on "The Care of the Patient." To illustrate his message, he related a personal story: the severe criticism he had received from his father, an eminent Harvard Medical School professor of his day, when he learned that his son, then an intern, had reluctantly acceded to the request of a patient to postpone for a few hours an operation for acute appendicitis. The patient had insisted that he must first attend to an urgent business matter. The operation eventually was successfully performed but this did not placate his father, and probably should not have. Wesselhoeft Senior was adamant that his son had not adequately carried out his professional responsibilities. Wesselhoeft Junior felt properly chastised and he ended his story by merely observing that he had learned an important lesson. He did not tell us, however, what he had learned. The questions that still nag me are these: Was the lesson so obvious and, if so, what was it; and what should he have done, beyond impressing on the patient the possible foolhardiness of his decision?

I touch on these experiences for many reasons: to impress upon you that I was educated at a time when I was admonished to prepare myself for my future professional responsibilities

by becoming as knowledgeable about our art and science as is humanly possible so that I could care for my patients. Conversing with patients -- to test my clinical judgment against their personal judgments -- however, was not part of my education, beyond learning how to take a careful history. To be sure those were the days prior to "informed consent", days when the idea of patient autonomy could not be found in the lexicon of medicine.

Yet, these were also the days when scientific medical research began to infiltrate medical practice on a scale unprecedented in the prior history of medicine. Consider that in 1945 NHI's research budget was approximately \$700,000, in 1955 36 million, and that today, in 1994, it is over four billion dollars. Should academic medicine have been more aware of the beginning radical transformation of medical practice and prepared us for our ethical responsibilities if we were to choose a career in research, particularly at an institution which encouraged us to do so? And irrespective of whether we would become practitioners or investigators, did we need to be educated for the new world of medicine in which the choice of therapy and/or research could be a fateful one for us and our patients? Only decades later would I appreciate that the ethics of practice and research have different dimensions. I shall return to all this.

To be sure, in the days prior to informed consent only a limited corpus existed on the ethics of human experimentation.

Among the rare documents is the one by our own Walter B. Cannon who had written in the Journal of the American Medical Association in 1916, in response to press criticism about controversial experiments conducted with syphilitic patients that

[t]here is no more primitive and fundamental right which any individual possesses than that of controlling the uses to which his own body is put. Mankind has struggled for centuries for the recognition of this right. ... Society as now constituted will obviously not countenance any operation performed for the satisfaction of the operator or for the assurance of the investigator, whether or not for the immediate benefit of others, unless the consent of the person on whom the operation is to be performed has previously been obtained.

Note Cannon's emphasis on patients' rights to control his own body.

Yet, in the same year the American Medical Association rejected a proposal to include in its code of ethics a provision stating that ethical human experimentation required the express consent of the patient-subject. A number of leading clinicians of that day were concerned that such a requirement would complicate the investigator-subject/physician-patient encounter and, thus, interfere with the practice of medicine and the progress of medical science.

These concerns were well founded. In the late 1960's, deeply immersed in my own explorations, it similarly dawned on me that research and practice had become so intertwined that many of the problems inherent in human experimentation could

not be resolved unless one first examined the professional attitudes governing clinical practice and, then, their impact on research. Recall Harvard's Talcott Parson: "[T]he doctor-patient relationship has to be one involving an element of authority-- we often speak of 'doctor's orders.'"

When I first, and most tentatively, began to question the assumption of doctors' sweeping authority in therapeutic decision making and its too unchallenged infiltration into the investigator-subject relationship, many of my medical colleagues became even more upset than they had been earlier when I had addressed them on my views on the ethical conduct of human research. They cautioned me that if I were to persist I would open up for inspection even thornier issues than I had in the past. I persisted and eventually published a book on the physician-patient relationship: The Silent World of Doctor and Patient.

My colleagues' concerns reside in physicians' conviction, succinctly expressed by Andrew Ivy, that "the therapy of disease is, and will always be, an experimental aspect of medicine. We frequently forget ... that a patient is a voluntary experimental subject of the physician." I believe Ivy spoke here to the vast uncertainty inherent in the practice of medicine, so eloquently brought to our attention years later by Lewis Thomas when he wrote that "twentieth century science [confronts] us with the depth and scope of [our] ignorance." Unlike in the past, he went on to say,

"[w]e are at least facing up to it. [In earlier times] we either pretended to understand how things worked or ignored the problem or simply made up stories to fill the gaps."

Research seeks to penetrate and resolve our ignorance and to do so requires human beings as subjects. But scientific research, as I shall soon argue, is an enterprise different from the kind Ivy talked about when he equated therapy with experimentation. For the moment I want to flag two issues: (1) In therapy, the physician has the interests of his or her patient solely in mind, while in research physician-investigators are double agents with commitments both to their patients and to science; and (2) in therapy, physicians persist to this day in "mak[ing] up stories to fill the gaps," however responsibly informed also by clinical experiences and clinical judgment. The unresolved problems of medical uncertainty and how to communicate it continue to dispose physicians to practice medicine on their own authority, because sharing their uncertainties with patients runs so counter to their professional convictions. This is true even now in the post-1957 world of informed consent. Physicians may talk more but what they communicate is not in the service of making patients fuller partners in the decision-making process. I note these two issues in order to impress upon you that doctors have been unprepared and unwilling to think seriously about the ethics of research because they intuited that it would inexorably compel them to think seriously about

the ethics of clinical practice.

Ivy, who also had been the chief medical "prosecution witness at the Nuremberg trial of the Nazi physicians, asserted then, as he did later in his writings, that "[t]he fact that the patient is always to some extent an experimental subject of the physician is the reason that Hippocrates formulated his famous Oath for Physicians." Perhaps Hippocrates intuited that medical uncertainty required him to admonish physicians to be most careful in selecting the appropriate therapy, "to abstain from whatever is deleterious or mischievous," and to "above all do no harm." The Hippocratic Oath, however, is not, as Ivy suggested at the Nuremberg Trial, a testament to how physicians should "treat their experimental subjects," if only because the Oath says nothing about consent, if only because in other Hippocratic writings no exception was made for research when Hippocrates admonished doctors "[to reveal] nothing of patient's future or present condition."

To return to my student days at Harvard: I was educated at a time when physician-investigators did not think deeply about the ethics of research. I learned nothing about all this, even though in December 1946, when I was a second year medical student, some of the Nazi physicians who had conducted research on Jews, Gypsies and other political and military prisoners were placed on trial at Nuremberg. That news did not travel to our lecture halls. I learned nothing about this

chapter in the history of human experimentation, or the implications of the Nuremberg Code promulgated by the Allied Military Tribunal for the future conduct of research. Only a decade later, once I had joined the Yale Law School faculty, did I become aware of what had transpired at Auschwitz and in other concentration camps.

Even if the Nazi experiments had been brought to our attention, probably not much would have been made of them in terms of their relevance to contemporary research practices. Since the experiments had been conducted with a brutality and utter disregard of human decency unparalleled in the history of medicine, what transpired at Auschwitz would have been viewed as it still is, in the words of Prosecutor Telford Taylor, as evidence of "the ravages of Nazi pseudo-science." From the perspective of sadism, this is of course a correct assessment. Yet, I soon began to wonder whether the emphasis on the atrocities also served as an excuse not to learn important lessons which the Nazi experiments pose for our time, lessons that can become most starkly illuminated when research is conducted without any veneer of civility. The revelations at Nuremberg and the Nuremberg Code deserved detailed exploration then as they still do now.

Had my teachers shown an inclination to explore these problems with us, they would have found some, but not many, documents that could have served as a basis for class discussion. Though human research dates back to medical

antiquity and surely captured the imagination of academic physicians at an ever accelerating pace since the mid-nineteenth century -- the beginnings of the age of medical science -- scant attention had been paid to the ethics of research. References are sparse: In 1809, the English physician Thomas Percival published his code of medical ethics. There he alluded briefly to medical experimentation in the context of innovative treatments: "[I]f ordinary modes of practice have been attempted without success, it is for the public good, and in special degree advantageous to the poor (who, being the most numerous class of the society, are the greatest beneficiaries of the healing art) that new remedies and new methods of surgical treatment should be devised. [But] no such trials should be instituted without a previous consultation of the physicians or surgeons ..." He said nothing about consulting patients. The American Medical Association adopted Percival's Code in 1847 as its Principles of Medical Ethics, but omitted any of his references to human experimentation.

Nor did Claude Bernard in his 1865 book, An Introduction to the Study of Experimental Medicine mention consent. He affirmed "the duty and right ... to perform an experiment on man" and admonished physicians that "Christian morals forbid only one thing, doing ill to one's neighbor so that experiments that cause only harm are forbidden." William Beaumont in 1833 mentioned voluntary consent as a necessary

requisite for the conduct of research. His doing so was preordained since he drafted his code specifically for his experiments with the alert and competent Alexis St. Martin whose open fistula tract allowed Beaumont to study the physiology of the stomach over an extended period of time. There are two ironic exceptions to this scant history. In 1900, the Prussian Minister of Religious and Medical Affairs, and in 1931 the German Reich Minister, promulgated rules for the conduct of research that in part were even more stringent than those of the Allied Military Tribunal.

Of course, my medical school teachers could have drawn on their own personal experiences as investigators in exploring with us the ethics of research. Beyond that, they might also have drawn on their experiences as senior advisors to various governmental agencies which had become involved, for example, in human radiation research as soon as World War II was transformed into the Cold War. In reviewing the documents so far made available to the Presidential Advisory Committee, I came across the names of a number of my teachers who had chaired or served on joint panels that sanctioned, or at least acquiesced to, the deliberate exposure of civilians and soldiers to atomic radiation, radioactive tracer studies with mentally retarded children at the Fernald School of this city or with pregnant women at Vanderbilt University, total body irradiation studies with terminally ill cancer patients at Cincinnati and elsewhere, or so-called "experiments of

opportunity" with Navaho Indians working in uranium mines.

Last month our Advisory Committee released its Interim Report on the Human Radiation Experiments. We noted repeatedly the surprising fact that during the decades these experiments had been conducted, "the government engaged in high-level debates on human experimentation ... and [issued] policy statements." We do not know much about the depth of these debates. From what we know so far, I believe that a New York Times article overstated the case when it averred that we have "traced the almost continuing jostling between the military's desire for data on radiation and the ethical scruples of some senior officers," and that the question "whether it is possible to offer a patient honest treatment and experiment on him at the same time appears to have been a consideration in even the earliest documents of Cold War experiments."

In perusing the minutes of the meetings during which the use of human beings for radiation research was discussed, I found evidence neither of any sustained exploration of the ethics of human research nor of any protracted attempts to specify criteria for providing protection for the subjects of research. To be sure, one can discern uneasiness over the use of human beings, but disquiet quickly yielded to the felt necessity of finding answers to important military questions about the impact of radiation exposure on the fighting effectiveness of soldiers. Again and again I was struck by

the reluctance to confront the ethical implications of using human beings for our ends, and by the readiness to dispose of such concerns by resorting to such banal statements as "I don't like it." Not probing ethical obligations to human beings more deeply soon led to troubling practices such as intentional releases of radiation over populated areas in various states of the United States, plutonium ingestion experiments with mentally retarded children, etc., etc.

Illuminating are the prolonged debates that all too quickly polarized around the question of whether human studies should be initiated at all or whether they must proceed with all deliberate speed. Dr. Wallace Fenn of the University of Rochester School of Medicine emerged as the most remarkable spokesperson for delaying any human research. He insisted, most generally, that the use of human beings for others' ends is a dangerous road to embark on and, more specifically, that insufficient animal research had so far been conducted so that it was unwise to proceed to human experimentation. Nothing came of his objections and he cast a lonely vote against ratifying a recommendation "to obtain all necessary scientific information, including if necessary, human experimentation under established principles of such experiments."

Had the debate not polarized around whether or not to conduct any human research, Fenn's cautionary comments might have received more careful attention. From the beginning, it should have been clear to all participants that human research

should and would have to be conducted and that the questions before the committee were not whether it should be conducted but how, for example, in what numbers, with whom, and with what safeguards. Moreover, the problem raised by Fenn and others about the need for prior animal experimentation should have moved the committee to establish criteria on the extent of such research, and with what kinds of lower and higher species of animals. Furthermore, "the established principles" to which the Committee referred in its eventual endorsement of human experimentation would on thoughtful inspection not have been found very helpful. The principles embraced were the three niggardly principles of the AMA's Judicial Council: (1) voluntary consent, (2) prior animal experimentation, and (3) proper medical protection and management. What constitutes voluntary consent, and after what kind of disclosures, was never discussed. Indeed, whenever the recruitment of volunteers was mentioned, any discussion immediately moved to whether they should receive hazardous duty pay or be compensated in other ways.

Issues that today we would consider of ethical significance were cursorily mentioned in the Committee's deliberations. Since they were never identified as such, they could not be probed in any depth. For example, concerns were raised about the long-term effects of radiation exposure, i.e., the increased incidence of leukemia and cancer. The responses were these, "The fact that [he] may get cancer 20

years later is just of no significance to us ... What we are interested in is what level [of exposure] is going to make the men sick or non-effective within a period of 30 days." Nobody objected, beyond noting that this was "a problem" and that "we are willing to take a chance." For the important problem was, "where are we going to get the best information in the most scientific manner." As one physician-colonel put it, "of course we are [concerned] about long-term effects from a national viewpoint and the Armed Forces are part of the nation, but [in instances] of war, attention is paid to [such matters] certainly not beyond five years and in that period, human beings are not taken into consideration ... and you can't accomplish missions without things like that happening."

Not surprisingly, the question was raised whether "top level agreement and approval" must be obtained before proceeding with radiation research. The answer was this: "No, I don't think so. I think that is the point in error here. Because actually when you take a subject of this type and put it up for top level agreement on human experimentation, then that throws open the whole problem, particularly at political levels where human experimentation has to be agreed upon ... I think we should go ahead and do the work and not talk about it. [We sought approval once] and the political decision was that you couldn't do it. Now unquestionably if the same subject comes up at a political level you are going to get the same answer every time." End of discussion.

Finally, proposals for conducting radiation experiments with cancer patients were also entertained: "Why aren't we justified in selecting a group of individuals that would have to have this therapy?" The question was left hanging in midair even though this was a moment when one of the many physician-members of the committee might have commented on the propriety of using terminally ill patients for army research purposes. The only major concern raised was this: that data on the impact of radiation on debilitated patients may not be comparable with its impact on healthy soldiers.

This was by-and-large the sum and substance of the "ethical" debate.

It is not surprising that the ethical imperatives which should guide human research with patients or normal volunteers were not explored except for sound bites here and there. Of course, we had the Nuremberg Code, and thereby hangs a tale. Here is what happened: In 1953, the Secretary of Defense, Charles E. Wilson, issued a memorandum that adopted the Nuremberg Code for the conduct of research in the military establishment. As yet, we have not located documents that reveal what prompted the Secretary in the first place to promulgate regulations on human research. Perhaps he had become aware of the diffuse concerns raised in recent years about human experimentation and therefore wanted to establish a coherent policy for DOD. We do know, however, that a prior draft document on DOD regulations for human research had been

circulated and that soon thereafter Stephen Jackson, one of the Defense Department's lawyers, suggested that the adoption of the Nuremberg Code would better serve the Department of Defense's purposes.

To be sure, if one wishes to, one can make much of this policy statement. After all, it was signed by the Secretary and thus can be construed as official and legally binding. Lawyers may wish to make much of this fact and question the relevance of my contention that neither the Secretary nor those who submitted it to him were aware that in its present form, without any detailed commentary, the adoption of the Nuremberg Code could not serve any useful purpose. I am surprised that the lawyers who reviewed the document did not comment on the vagueness of the principles for purposes of implementation.

Perhaps it was an expression of unconscious wisdom or an indication of the four Armed Forces Secretaries' lack of enthusiasm over the proposed policy that led to the memorandum being stamped, as soon as it was born, "Top Secret," thus making it unavailable for a while to those most involved in human research. Consider also that the Nuremberg Code, except by order of the Secretary of Defense, had been adopted by no one: not by the American Medical Association, not by the World Medical Association. Henry Beecher and others had criticized the Code severely for its deficiencies as a code of ethics for the general conduct of human research. Perhaps their

criticism was too sweeping but they were correct in arguing that the Code required amendments, additions and particularly extensive commentary before it could become a viable guide.

The ten principles begged for commentary. For example, provisions needed to be drafted on the extent and depth of animal experimentation, with what species, prior to initiating human studies; on the kinds of disabling injury, a priori feared to occur, that should preclude human experimentation; on the limits of investigators' discretion to weigh the humanitarian importance of research in a cold war climate against physical and dignitary injuries to subjects of research.

The ten principles of the Nuremberg Code speak to all these and other issues but, except for Principle I, without any elaboration. I wrote about all that 25 years ago: "[C]odes, as long as they stand alone and are not surrounded by detailed commentary, are pious exercises in futility. Since they aspire to ideals and are divorced from the realities of human interaction, they invite judicious or injudicious neglect. If codes are to have meaning, they must be tied to procedures that permit constant interpretation of [lofty principles]."

Thus, I find the Secretary's 1953 memorandum a starting point but no more than that. When, prior to its enactment, it was presented for comment to the Committee on Chemical Warfare, Dr. Henry Johnstone observed, "[i]f they can get any

volunteers after that, I'm all in favor of it." Everybody laughed, followed by silence. His derisive observation speaks to his unwillingness to take the Code seriously. Johnstone and his colleagues intuitively recognized the problems it would pose for the customary conduct of research which till then had given investigators unfettered discretion. This was enough to dismiss it.

The Advisory Committee, in its Interim Report, stated that "a cornerstone of modern research ethics is the requirement that research proceed only with the informed consent of a competent subject." This is the cornerstone of the Nuremberg Code but it is a cornerstone not yet firmly in place, not yet sturdy enough to carry the weight of its assignment. In the remainder of my talk I want to support this contention from a number of perspectives.

I begin with the Nuremberg Code, its majestic first principle -- "the voluntary consent of the human subject of research is absolutely essential." The judges at Nuremberg set forth this principle in most uncompromising language. They were shocked, as was the world community, by the revelations of the Nazi concentration camp experiments, embedded as they were in the extermination of millions of Jews, Gypsies and other lives deemed not-worth-living. But the experiments also created their own shock waves in the medical community because they had been conducted, condoned, and embraced by German medical scientists of international

renown.

How could medicine have descended to such an abyss? Any answers to this question must consider the arguments advanced at the trial by the German physicians in justification of what they had done. They illuminate past and present problems inherent in all human research: National necessity and the exigencies of war which also compelled the U.S. mustard gas experiments during World War II and the radiation experiments during the Cold War; the use of lives not worth living, lives condemned to death, to find answers as expeditiously as possible to wage offensive and defensive war, which in language less stark, have been proffered to justify the use of lives-soon-to-expire in total body irradiation experiments with terminal cancer patients; the need to modify and dispense with consent in order to advance science for the benefit of mankind because nobody "would volunteer for [certain] experiments." This was the way the concentration camp experiments began when Sigmund Rascher asked Heinrich Himmler for "three political prisoners" to conduct high altitude experiments, or the way U.S. Army researchers saw it when they essentially abrogated consent during the mustard gas experiments by arguing that one must not disclose too much to the soldiers because this would frighten them. I could go on, but I hope I have said enough to support one contention: that for the sake of humanity, it is important to learn how far we can go in the conduct of research without voluntary consent.

For once that step is contemplated, and then taken without carefully and stringently limiting it, we endanger our and our subjects' humanity.

In most uncompromising language the first principle of the Nuremberg Code seeks to safeguard our humanity. The judges not only spoke about "voluntary consent" but also rigorously defined how they wanted investigators to interact with subjects in the future: Investigators must not resort to "force, fraud, deceit, duress, overreaching or any other ulterior form of constraint or coercion," and the subject must understand "the nature, duration, and purpose of the experiment ... all inconveniences and hazards reasonably to be expected and the effects upon his health or person which may possibly come from his participation in the experiment." Let me only note in passing that the commentary on Principle I was soon compromised. In 1962, the Army regulations on research provided new commentary: "He must have [only] sufficient understanding of the implications of his participation to enable him to make an informed decision, so far as such knowledge does not compromise the experiment [or] invalidate the results."

The Nuremberg judges appreciated that their principle was not grounded in medical research ethics but in legal ethics: "Our judicial concern, of course, is with those requirements which are purely legal in nature.... To go beyond that point would lead us into a field that would be beyond our sphere of

competence."

Implicitly the judges invited the medical profession to modify their Code so that it would also comport with those requirements which are medical and scientific in nature. The World Medical Association responded to this invitation when it promulgated its Helsinki Code and in the process consent was stripped of its preeminence. The medical profession has found it most difficult to come to terms with the nature and quality of consent that should govern human research. The Nuremberg Code disturbed the conscience of investigators, but at first not too much. Recall that the radiation experiments were conducted after Nuremberg. Yet, and this should come as no surprise, during the Advisory Committee's hearings we have heard testimony that investigators should not be faulted for conduct that predated the legal requirement of informed consent, echoing similar defenses raised when in 1972 my fellow Panel members and I investigated the Tuskegee Syphilis Study. To the extent such a defense has merit, it only demonstrates that investigators too were victims of unexamined practices. This should not exonerate the research community completely but, to return once more to the radiation experiments, if it were true, as alleged in the headline of the New York Times article, to which I have already referred, that the "Panel finds wide debate in the forties on the ethics of radiation tests," then physician-investigators would be more culpable than I find them.

It is a separate matter that in contemplating the radiation experiments, governmental agencies and their lawyers were not more attentive to fundamental jurisprudential values inherent in our Constitution and Bill of Rights. The documents which we have examined so far only reveal their concerns over tort liability, and not over the jurisprudential implications of the contemplated radiation research. The lawyers who were consulted were unmindful of Justice Cardozo's pronouncement in 1916, which 41 years later would become the jurisprudential cornerstone of the doctrine of informed consent, that "[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body."

The Nuremberg Code anticipated this jurisprudential development. In their uncompromising language, as I have already suggested, the judges expressed their thoroughgoing commitment to basic Anglo-American jurisprudential principles of individual autonomy and self-determination; and in their commentary on Principle I, they emphasized both the mindset (i.e., no duress or overreaching) which investigators must bring to their disclosures as well as the nature and quality of their disclosure obligations. To put this another way, the judges commanded investigators to take subjects' self-determination most seriously and then emphasized less subjects' consent but the physicians' disclosure obligations. The judges may have been aware that consent is difficult to

define and to ascertain. Thus, they may have thought that if investigators come to the task with thoroughgoing commitments both to autonomy and to full disclosure, consent would be adequately safeguarded. They did not, and they did not want to, consider that such commitments would place great strains on the pace of research and impose great psychological burdens on investigators by asking them to be much more forthcoming about everything they want their subjects to submit to for the sake of research and human progress. These major implications of voluntary consent, or what is now called informed consent, the research community was and is reluctant to accept and, therefore, informed consent has only gained a precarious foothold in the world of human experimentation.

The 1973 Federal Regulations for informed consent in research have improved matters but formidable problems remain. They reside in informed consent's parentage. One set of parents were the Nuremberg judges and the other the common law judges who in 1957 promulgated the doctrine of informed consent for therapeutic settings. I cannot discuss with you this afternoon all that needs to be said of this doctrine. Most importantly, you must appreciate that the doctrine is most limited in scope. The doctrine was intended to limit physicians' tort (malpractice) liability whenever patients allege that they had been inadequately informed about therapeutic risks, benefits and alternatives. It was designed to specify those minimal disclosure obligations that

physicians must fulfill to escape legal liability for alleged non-disclosures. Even though the judges based the doctrine on "Anglo-American law[']s] premise of thoroughgoing self-determination," competing considerations of tort law, i.e., to restrict physicians' financial liability, greatly limited the new disclosure requirements; thus making them unresponsive to the doctrine's underlying idea that patients must from now on be viewed as autonomous participants in the medical decision-making process. While physicians grudgingly bowed to the doctrine's formal requirements in order to escape tort liability, they rejected, aided and abetted by law, its underlying idea of shared decision making. Again, it should come as no surprise that physicians have frequently asked, why comport with a requirement when we can easily tailor the disclosures, we are now mandated to make, so that patients will agree to what we wanted them to accept in the first place? In putting it that way, physicians, of course, disregard the idea which I believe underlies the doctrine: to give patients a more meaningful voice in the medical decision-making process. It is a pity, but also a fact, that informed consent has remained a defensive doctrine and not become a Magna Carta for a radically altered physician-patient relationship. Informed consent in research, originating in, and transported from the context of therapy, suffered a similar fate.

I have already suggested that the Nuremberg Code made no

significant impact on improving disclosure and consent practices for research, at least until 1973. Consider that the Tuskegee Syphilis Study which began in 1932 continued on its not so merry way until 1972. Only then did the DHEW Advisory Panel, on which I served, terminate the Study. The revelations of what had transpired in Macon County, Alabama, and our recommendations for policies that in the future should guide human experimentation, led in 1973 to the Federal Regulations for the Protection of Human Subjects of Research and to the establishment of two Commissions that enriched the discourse on ethical research. One of the Commissions was chaired by Kenneth Ryan and he deserves our gratitude for having elevated the discussion on research ethics to new heights. The Federal Regulations of 1973 essentially required that institutions engaged in research provide assurances (1) that they had adopted a statement of principles for protecting the rights and welfare of subjects; (2) that it had established an Institutional Review Board (IRB) which will review research protocols and then either approve, seek modifications, or disapprove them; and (3) that the IRB and investigators had paid careful attention to the new and more detailed requirements for informed consent.

Thus, the Federal Regulations for the Protection of Research Subjects gave primacy to informed consent and assigned to investigators and IRBs the responsibility for implementing these requirements. Before commenting on the

fate of these regulations, let me note that in my early work on human experimentation I identified as central "problems for the conduct of research the inherent tensions between the advancement of science and the inviolability of subjects of research. I argued that informed consent will only become a meaningful requirement once investigators accept its underlying premises: autonomy and right to self-determination. I believed then, as has now been so succinctly stated in the Advisory Committee's Interim Report, that "[a] cornerstone of modern research ethics is the requirement that research proceed only with the informed consent of a competent subject."

While I was aware that disclosure of information would have to be a sine qua non to achieve this objective, I did not then appreciate fully the painful burdens which a requirement to be utterly truthful would impose on investigators: i.e., to take the necessary time for extending the invitation; to apprise subjects of matters that might prove to be anxiety-provoking but had to be presented if truthfulness is the polestar; to take the risk that too many subjects might refuse participation for well- or ill-considered reasons; to become resigned to the possibility that the pace of research may slow down or that some research projects may be impossible to conduct.

I also did not fully appreciate, as I have already suggested, the extent to which investigators' thinking about

their obligations to disclose is shaped by their caring, yet authoritarian, attitudes toward patients. a legacy of the millennia-old ideology of Hippocratic medicine. Investigators may now appreciate better than they did in yesteryear that the goals of medical practice and scientific research are different, that in the latter subjects also serve as means for scientists' and science's ends. Yet, investigators have not pondered in sufficient depth Kant's admonition not to use persons as means for others' ends, otherwise they would have begun to reconsider the shortcuts they take in obtaining informed consent process out of a felt need to advance science or the rationalizations they employ when they justify such conduct by pointing to similar practices in therapeutic settings. The two situations are not comparable.

Thus, what has happened since 1973 is this: The requirements for informed consent are being met by formally complying with their stated criteria, setting them forth in the protocols and in the informed consent documents signed by subjects. As a consequence the forms have become so detailed, so replete with scientific information, that they are all too often incomprehensible. But there is more to this story: First, the mass of data provided obscure vital information a subject needs to have in order to arrive at considered judgment about participation. Second, the criteria which would give subjects the best understanding of what they are agreeing to are often not clearly set forth. Most members of

IRBs with whom I talked have voiced concerns over the flawed nature of the informed consent process. They are aware of protocols and consent forms in which the risks of participation are minimized; in which the unlikelihood of anything of benefit accruing to individual patient-subjects is obscured. Beyond that, they are aware that during the oral informed consent process patient-subjects are subtly or not so subtly coerced to participate; that the short period of time allocated to obtaining informed consent makes it doubtful whether patient-subjects fully appreciate to what they are consenting; or, since all too often too few subjects refuse participation, that something must be wrong with the informed consent process.

The pressures which the quest of advancing medical knowledge poses for the informed consent process are enormous, as are the pressures exerted on institutions and investigators by drug and medical devices companies to test their products on patient-subjects for the sake of progress and profit. And so are the pressures on investigators to complete their research projects for the sake of priority of discovery, advancing their careers, maintaining their laboratories and staff, and obtaining future grant support. These problems should not be dismissed lightly by espousing ethical ideals and pious condemnations. But these realities should not keep us from recognizing that informed consent is not the safeguard for protecting the rights and welfare of research subjects

that it is claimed to be.

Some years ago, I received a call from a principal investigator of one of the many multi-center projects that are now the vogue. His ethical problem was this: Apparently in a randomized study designed to compare the respective effectiveness of a surgical and medical intervention, he and his collaborators wanted to assign by lot patient-subjects to one or the other arm of the study. They soon found out that too many patient-subjects refused participation, thus endangering by virtue of selection bias, the validity of any results. He asked whether it was ethical to tell potential subjects that they will be assigned to either treatment according to their medical needs, even though they would still be chosen by lot? I responded that I did not know whether it was ethical or not but that he would be lying. He became annoyed, chiding me that I did not understand that the research was important and could not be carried out unless a subterfuge was employed. That was precisely the reason, I told him, why I had answered him as I had. In light of the competing ethical tensions, I could not say whether what he contemplated to do was ethical or not; I could only say that he violated one ethical command, not to lie to his subjects, but for the sake of another ethical principle, to advance knowledge in the face of uncertainty. The experiment eventually was carried out using a subterfuge that had been approved by the IRBs at the various medical centers. The

study led to important advances in the treatment of a common disease.

I once thought that informed consent could, should, and would safeguard the rights of research subjects. It can only do so, however, if the principle of respect for individual autonomy becomes the cornerstone on which informed consent will rest. Fidelity to that principle provides the best guarantee for controlling the exercise of the kind of professional authority that traditionally has led to decisions for, rather than with, patients. Here, and only in passing, I must call your attention to the fact that throughout I have talked about respect for autonomy in individual patient-subject/ physician-investigator interactions. I have left unconsidered the implications of societal judgments, for example with regard to health care, that may be based on giving greater weight to communitarian values than individual rights. These issues I cannot explore this afternoon.

Taking stock of the current scene, I believe that much too much is being made of the safeguards provided by IRBs and the requirement of informed consent in protecting the rights of research subjects. I now have come to believe that it will take a long time before informed consent can fulfill this promise, and it will not happen until physician-investigators become committed to the primacy of the principle of respect for person. To accomplish that objective requires first of all a massive re-education of physicians, beginning in medical

schools.

In conclusion, this my plea for education takes me back to Harvard Medical School. Harvard University Press was kind enough to allow me to read page proofs of a forthcoming book, co-authored by Dean Daniel Tosteson and his associates, New Pathways in Medical Education: Learning to Learn at Harvard Medical School. It is a wonderful and thought-provoking book about the trials, tribulations and achievements of introducing a new curriculum at our school. It will surely be read and pondered by medical educators throughout the United States and prove to become the Flexner report for the 21st century. I cannot convey to you this afternoon the book's important messages beyond noting its student-centered approach, its long overdue call for rewarding faculty teaching and not only faculty research, its emphasis on preparing future physicians for the challenges spawned by medicine's spectacular scientific and technological advances as well as by the ever-increasing economic costs that as a nation we may not be able to afford.

The book convincingly argues that the medical school curriculum must be reformed in light of the 20th century's scientific and technological revolutions which have so fundamentally changed the practice of medicine. Yet, the book pays scant attention to two other revolutionary developments and their implications for the education of medical students: Law's impact on the doctor-patient relationship and the impact

of medical research on the practice of medicine. In the various discussions throughout the book on the doctor-patient relationship, I found repeated references to practical considerations: Teaching students skills of educating and counselling patients, being attentive to psychological disturbances and psychiatric illness, relating better to patients' psychosocial concerns and problems. However, I found only one brief specific reference to exposing medical students to the philosophical, ethical and legal issues, which we can no longer avoid facing as practitioners and investigators. The reference is this: "Students and faculty [must] analyze the personal and ethical implications of commonly encountered clinical dilemmas, such as informed consent or defining the appropriate care for terminally ill patients." I was struck that in this singular reference to informed consent it is identified as a "clinical dilemma," which, of course, it also is. But it is not identified as a professional dilemma, both in light of law's new commands, embodied in the doctrine of informed consent, and in light of the increasing interplay between practice and research.

I hope that these matters too, if they have not already, will find their rightful place in the new curriculum. I highlight these possible lacunae because in my interaction with medical students and faculty, I generally have encountered considerable resistance to exploring these problems which, of course, add new burdens on learning how to

become a professional in the waning years of the 20th century.

While working on this lecture, my thoughts often took me back to the Talmud, to the encounter between Rabbi Hillel and a heathen who challenged the Rabbi: "Make me a proselyte, on condition that you teach me the whole Torah while I stand on one foot." Hillel responded, "What is hateful to you, do not to your neighbor; that is the whole Torah, while the rest is the commentary thereof: go and learn it." In all my work as a teacher and scholar, I have stressed, as Hillel did, the importance of commentary and learning. But I had not given much thought to the first part of Hillel's message, a variant of the Golden Rule, "What is hateful to you do not to your neighbor." I had accepted it as a given. But now it occurs to me that while such a rule may suffice for ordinary human interactions, it does not serve us well, without additional commentary, as a prescription for the interactions between physicians and patients or investigators and subjects. In these encounters, throughout the millennia of medical practice or during the last 150 years of medical research, physician-investigators have rarely considered that their practices have dimensions which they should view perhaps not as hateful but at least as nonacceptable, unsatisfactory, harmful and hurtful. Instead, they have taken on faith that the ways in which they interact with patients and subjects are in accord with the Golden Rule. Yet, should we begin to wonder whether

our traditional propensity to take patients into our custody, however caring, rather than granting them the liberty of sharing the burdens of decision with us, ought not to become "hateful" to us? I leave you with this question. There is much to be pondered here.

I admit that I was eager to accept your invitation. Forty-five years ago you admitted me, a refugee from Nazi Germany then 5 years in this country, to this great school. You taught me well and what you taught me allowed me to go on learning. In giving this talk I wanted to repay in small measure the debt I owe you. I hope you will accept this my gift to you as an expression of my gratitude and thanks.