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Other People's Bodies: Human Experimentation on the 50th Anniversary of the Nuremberg Code

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8. *The Heroic Physician In Literature: Can The Tradition Continue?* presented by Anne Hudson Jones, May 12, 1993, in Louisville, Kentucky.

9. *'The Leaven of Science': Osler and Medical Research* presented by David Hamilton, May 10, 1994, London and Oxford, England.

10. *A Body of Knowledge: Knowledge of the Body* presented by Sherwin B. Nuland, May 10 1995, Pittsburgh, Pennsylvania.

11. *Other People's Bodies: Human Experimentation on the 50th Anniversary of the Nuremberg Code* presented by David J. Rothman, April 25, 1996, San Francisco, California.

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The Eleventh
John P. McGovern Award Lecture

Other People's Bodies: Human Experimentation on the 50th Anniversary of the Nuremberg Code

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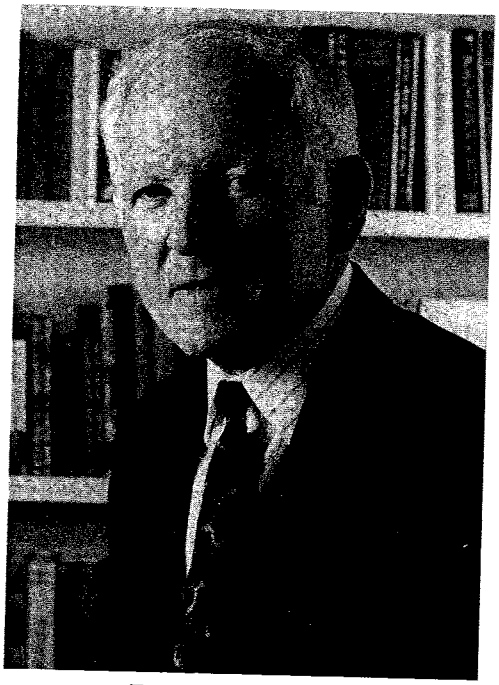

David J. Rothman

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Trained in social history at Harvard University, he has explored American practices toward the deviant and dependent. His study of the origins of mental hospitals, prisons, and almshouses, *The Discovery of the Asylum* (1971), was co-winner of the Albert J. Beveridge Prize of the American History Association. He continued tracing these events in *Conscience and Convenience: The Asylum and Its Alternatives in Progressive America* (1980). Together with Sheila M. Rothman he analyzed the process of deinstitutionalization in *The Willowbrook Wars* ' (1984). In 1996, he co-edited with Norval Morris, *The Oxford History of the Prison*. In 1987, he received an honorary Doctor of Law Degree from the John Jay School of Criminal Justice.

In 1983, he joined the Columbia medical school faculty and in his recent work has addressed issues in the history of human experimentation, the history of drug regulation and clinical trials with a particular focus on AIDS, and the rationing of scarce medical resources. In the Spring of 1991, he published *Strangers at the Bedside; A History of how Law and Bioethics Transformed Medical Decision-making*. In the Spring of 1997, his new book, *Beginnings Count: The Technological Imperative in American Health Care* will appear. He is co-director of the Columbia-Montefiore Certificate Program in Bioethics and the Medical Humanities.

David Rothman is a member of the Board of Advisors of the Project on Death in America (open Society Institute) and is overseeing a multi-disciplinary history of death in America. He is also a member of the Board of Trustees of the Open Society Institute.

In the fifty years since the issuance of the Nuremberg Code, the ethics of human experimentation has assumed such centrality in social thought and public policy that it requires an act of imagination to recall just how novel this event was. Nuremberg represented the first attempt to set forth and enforce an explicit set of principles, literally a code, in the conduct of human experimentation. Whatever weaknesses commentators would later identify, and whatever refinements marked the content of successor codes, Nuremberg was the pioneer effort to implement standards that clinical investigators were required to observe. [1]

Its originality as a code notwithstanding, Nuremberg was certainly not the earliest effort to analyze the ethics of human experimentation. Already in the thirteenth century, the English philosopher Roger Bacon had explained that progress in medicine would never come as quickly as in the natural sciences because scientists could "multiply their experiments till they get rid of deficiency and errors." The physician, on the other hand, was unable to do this "because of the nobility of the material in which he works."[2] Over the years, many individuals proposed appropriate standards for investigators to follow and decried particular abuses in practice. But until Nuremberg, there was practically no professional or public governance of human experimentation.

Thus, to appreciate the degree to which Nuremberg built on past precedents and the degree to which it represented a novel departure, it is necessary to examine the state of clinical research and ethics before 1947. First, in terms of principles, what obligations did investigator owe the subject? What information was to be shared? What degree of consent, if any, was necessary? Second, in terms of practice, were the principles respected by investigators? Did they live up to the standards? Finally, to the extent that practice diverged from principle, what efforts were made at enforcing standards? Were penalties levied on errant researchers, either by legally constituted bodies or professional organizations?

All of these questions are of obvious relevance to the history of medicine. But no less important, particularly as we observe this fiftieth anniversary, they are essential to framing the contribution of the Nuremberg Code itself.[3] At the trial of the Nazi doctors, defense attorneys claimed that before World War Two the ethics of human experimentation were undeveloped, both in the United States and Germany. Principles of voluntariness and of consent, they argued, were poorly understood and usually ignored. American physicians, no less than German ones, paid no heed to consent and frequently carried out experiments on ignorant and unwilling subjects. These points certainly establish Nuremberg's novelty, but at the price of finding a fatal flaw in the prosecution of the Nazi doctors. Nuremberg becomes an exercise in ex post facto punishment, setting new standards and then imposing them on the defendants. To be sure, the conviction and punishment of the offenders could easily be justified by ruling that their acts were so horrendous that they constituted a crime against humanity. They had committed war crimes, including the murder of innocent civilians; indeed, the Nuremberg court offered this very judgment: "The record clearly shows the commission of war crimes and crimes against humanity". But instead of stopping there it continued on to address the issue of "Permissible Medical Experiments." Ultimately, it condemned the Nazi doctors for unethical research; they were guilty as physicians, not as civilians, of "violating moral, ethical and legal concepts," not in a more straightforward sense, of murder. Precisely why the court eschewed war crimes and addressed human experimentation as such has never been satisfactorily explained. But whatever the reason, the court's posture brought unprecedented attention to the ethics of human experimentation.

I. Ethical Principles in Human Experimentation before Nuremberg.

The modern history of the ethics of human experimentation begins with Claude Bernard's 1865 book, *An Introduction to the Study of Experimental Medicine.* No one more cogently than Bernard delineated the potential contribution that clinical research could make to medicine. So vital was it that Bernard regarded experimentation as the third pillar of medical knowledge. As he traced it, physi-

cians first based their treatments upon findings made through their senses, that is, what they saw and heard through direct and intimate encounters with the patient. They felt the pulse, noted the color of the face, examined the urine, and listened to the chest, initially by putting their ear to it, later by using a stethoscope. Physicians, Bernard continued, learned to do more than rely upon their senses. They also "observed," by which he meant that they grouped facts together and formulated hypotheses; they made predictions about treatment outcomes and then studied whether they proved right. In this way, observation was essential to determining which interventions were effective. From Bernard's perspective, however, this exercise was essentially passive. The physician stood back and collected data, wisely and shrewdly, but from a distance.

It was the third form of knowledge that Bernard celebrated, what might be called "active observation." To clarify its meaning and implications, Bernard invoked the French naturalist, Georges Cuvier: "The observer listens to nature; the experimenter questions [nature] and forces her to unveil herself." In his own terms:

> *Experimenters must be able to touch the body on which they act, whether by destroying it or by altering it, so as to learn the part which it plays in the phenomena of nature....It is on this very possibility of acting, or not acting, on a body that the distinction will exclusively rest between sciences called sciences of observation and sciences called experimental.*

The very language with which Bernard describes experimentation establishes its potency, not only in terms of its ability to create knowledge but to generate ethical problems as well. Bernard's experimenter "touches" parts of the body, not gently, but to destroy it or alter it so as to learn more about its biological function. In this way, the investigator forces nature to "unveil herself," and in the process, he himself becomes an aggressor, indeed, something of a molester as he strips nature of her secrets.[4]

Had Bernard stopped his analysis of clinical research there, the development of human experimentation in the nineteenth century would appear as an exercise in the ruthless accumulation of knowledge, one that was deaf to the decencies of humanity or principles of ethics. But Bernard went on, and after exploring the

epistemology and methods of clinical research, he declared in passages now famous:

> *Experiments, then, may be performed on man, but within what limits? It is our duty and our right to perform an experiment on man whenever it can save his life, cure him or gain him some benefit. The principle of medical and surgical morality, therefore, consists in never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science, i.e., to the health of others.*

Bernard provides a frank and full recognition of the power of human experimentation to do good and to do harm. And with this double-edged potential in mind, he insists that research must always be in the best interests of the subject. If an experiment has the potential to cure, it may be carried out. But if it has no therapeutic potential and may injure the subject, it must not be conducted, regardless of how important the findings might be for others.

Obviously, Bernard's maxims are not fully in accord with contemporary principles, particularly given the scant attention he paid to the idea and meaning of consent. But others among his contemporaries not only echoed his insightful judgments but on occasion went beyond them, incorporating principles of consent into their own frameworks.

This was certainly true of the great clinician, William Osler. Properly credited with bringing scientific methods into medical education and clinical practice, Osler, as would be expected, was fully appreciative of the vital role of human experimentation. In 1907, he addressed "The Evolution of the Idea of Experiment in Medicine," sounding very much like Claude Bernard, and when it came to consent, superseding him.[5]

Like Bernard, Osler emphasized both the enormous capacity of clinical medicine to generate new knowledge and its highly invasive characteristics. In his formulation, "Man can interrogate as well as observe nature," and through this process, lighten many of "the burdens of humanity." Even more consistently than Bernard, Osler believed that experimentation was part and parcel of the conduct of clinical practice. "Every dose of medicine given is an experiment as it is impossible in every instance to predict what the result may be. " Even so, he, too, insist-

ed on setting limits on human experimentation. First, experiments on man must never be carried out before they had been tried on animals. Second, and here he departed from Bernard, Osler not only ruled out non-therapeutic research but required investigators to obtain the consent of the subject:

> *For man absolute safety and full consent are the conditions which make such tests allowable. We have no right to use patients entrusted to our care for the purpose of experimentation unless direct benefit to the individual is likely to follow. Once this limit is transgressed, the sacred cord which binds physician and patient snaps instantly.*

In effect, Osler enunciated the principles of consent well in advance of this proposition in the Nuremberg Code.

The viewpoints expressed by Bernard and Osler were shared widely. In 1886, a less prominent Boston physician, Charles Francis Withington, published an essay entitled, *The Relation of Hospitals to Medical Education.* The position he advocated was regarded as so important that his contribution won the prestigious Boylston Prize from Harvard University. Withington posed the ethical question in terms of the "possible conflict between the interests of medical science and those of the individual patient, and the latter's indefeasible rights." He was not at all confident that investigators satisfactorily resolved the conflict, and in truth, he himself had some trouble drawing boundaries between the needs of science and the "rights" (his term) of patients. But in the end, he came down staunchly on the side of rights, to the point of suggesting a remedy of a patient "Bill of Rights" which would not be adopted for another 90 years:

> *In the older countries of Europe especially, where the life and happiness of the so-called lower classes are perhaps held more cheaply than with us, enthusiastic devotees of science are very apt to encroach upon the rights of the individual patient in a manner which cannot be justified. In this country, we are less likely to fall into this error than those living under monarchical institutions, but even with us it may be well to draw up, as it were, a Bill of Rights which shall secure patients against any injustice from the votaries of science.*

Withington insisted that patients had "a right to immunity from experiments

merely as such, and outside the therapeutic application. This right is one that is especially liable to violation by enthusiastic investigators." Researchers who wished to try a new drug had to rely upon volunteers. In his view, "They had no right to make any man the unwilling victim of such an experiment."* He then concluded with a sentence that encapsulated the core principals of medical ethics: "The occupants of hospital wards are something more than merely so much clinical material during their lives and so much pathological material after their death."[6]

Although other texts reiterating these same principles could be easily marshalled, these three make apparent that the ethical dimensions of clinical research were recognized by physicians who advanced the development of modern medicine.[7] Such a conclusion ought not to be surprising, for the bedrock principle on which they rested their analyses was as old as medical ethics itself: do no harm, neither to the patient nor to the subject. Experimentation was bound by the ethics of the doctor-patient relationship, which, as we shall see, was a useful starting point, although not an altogether adequate model upon which to base the regulation of human experimentation.

All these writings drew a sharp distinction between therapeutic and non-therapeutic research, and were far more concerned with the latter than the former. They had little difficulty in condemning non-therapeutic research, especially when it placed the subject-patient at risk. But what was almost completely absent from the analysis was a discussion of the ethical principles that should govern experiments with a therapeutic potential. What was the physician obliged to tell the patient about an experiment that might benefit him? Was consent required? Who was to make the calculus of risk of harm versus benefit of cure? By ignoring this set of issues and focusing so exclusively on non-therapeutic research, these commentators make the intent and motive of the physician-researcher the

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* Withington was also alert to the possibilities of non-therapeutic experiments on terminally ill patients. An investigator, he insisted, "has no right to take advantage of the patient's extremity to recommend a procedure which can have no other advantage than to enhance the operator's reputation for boldness."

critical determinant. Were he seeking new knowledge and not attempting to ben efit the patient, then he was obligated to share information with the subject and obtain consent. But were his intentions to cure or to treat, then apparently he did not have to divulge the facts or obtain the patient's acquiescence to the procedure. Thus, the position adopted (which would remain intact for many decades) was consistent with the tradition in medical ethics of trusting to the integrity of the physician, not requiring formal collegial oversight or consultation or the patient's agreement. So long as the researcher's self-styled purpose was to benefit the patient, he enjoyed an ample discretion unfettered by colleagues or patients. In brief, the mindset of the physician, not the autonomy of the subject, drove the ethical analysis.

II. The Practice of Human Experimentation before Nuremberg.

The uniformity that marked the discussions of the ethical principles in research disappears when one examines the actual practices of investigators, and the reactions to them by the medical profession and the public. Here one finds countless examples of research conduct that blatantly violates the prevailing ethical norms. In a similar vein, one finds some observers outraged by the transgressions and others far more complaisant. The one generalization that can be offered is that no matter how grievous the ethical misconduct in research, professional disciplinary action or some collective expression of censure or disapproval almost never occurred. With a handful of exceptions, investigators who freely disobeyed all the norms set forth by a Bernard or an Osler paid no price for it.

The historical record, particularly as explored by Susan E. Lederer, makes abundantly clear that many investigators demonstrated scant regard for the rights or well-being of subjects. They conducted non-therapeutic research on unknowing or incompetent persons, putting them at risk and causing direct and serious harms. In 1904, a southern physician, Claude Smith, purposefully infected blacks with hookworm to study the transmission of the disease and did not give them the slightest hint as to what he was actually doing. "The patient," Smith stated in his published report, "seemed to have an idea that it was some medicine preparatory to the operation, as nothing was said to him about it."[8] In 1883,

George Fitch, resident physician at a Hawaiian leper colony, purposely infected some unknowing 18 leprosy patients with syphilis to prove the similarities between the two diseases.[9] Another of his colleagues infected relatives of leprosy patients who themselves were free of the disease with the leprosy organism to study transmission. "A splendid field for experimental work was at hand," he candidly wrote, "and stretching all questions of professional ethics, I did not hesitate to avail myself of the opportunities afforded me for testing the inoculability of leprosy."[10]

Some research protocols inflicted such egregious harm on subjects as to earn the condemnation of other investigators. The research by the Italian bacteriologist Giuseppe Sanarelli was a case in point. To prove that he had isolated the bacillus that caused yellow fever, he infected five Montevideo hospital patients with it and claimed (mistakenly) that he had produced the disease in them. William Osler led the attack on the ethics of his research: "To deliberately inject a poison of known high degree of virulency into a human being, unless you obtain that man's sanction, is not ridiculous, it is criminal."[11] In a later and fuller elaboration of this point, Osler explained:

> *The limitations of deliberate experimentation upon human beings should be clearly defined. Voluntarily, if with full knowledge, a fellow-creature may submit to certain tests, just as a physician may experiment upon himself. Drugs, the value of which has been carefully tested in animals and are found harmless may be tried on patients, since in this way alone may progress be made, but deliberate experiments such as Sanarelli carried on with cultures of known and tested virulence, and which were followed by nearly fatal illnesses, are simply criminal.*[12]

In much these same terms, Osler, and many other colleagues as well, condemned the cancer research that had been conducted by two German surgeons, both of whom took malignant cells from the diseased breast of a patient and injected them into the other, healthy, breast, to study the transmissibility of cancer cells. The *Journal of the American Medical Association* reported the incidents, applauding the subsequent refusal of a French medical academy to discuss the findings because they were obtained in so unethical a fashion. It hoped that "the

storm of indignation which has been aroused, shall deter others who might have in view, in their zeal for science, [conducted] similar unjustifiable experiments."[13]

The roster of non-therapeutic research on uninformed subjects could be extended almost indefinitely. In 1911, Hideyo Noguchi injected several hundred residents of a New York orphan asylum with an experimental substance, luetin, to learn whether it might serve to indicate the presence of syphilis. Other researchers used orphans to test the efficacy of tuberculin as a vaccine against tuberculosis as well as to trace the development of such dietary deficiencies as scurvy. So too, researchers subjected black infants at an Atlanta, Georgia hospital to lumbar punctures without the permission of their parents. One investigator even went so far as to infect an infant with the herpes virus for experimental purposes. As with orphans, prisoners were used as subjects in non-therapeutic and harmful protocols, including one protocol that imposed a diet designed to cause pellagra, and another that injected ameba in order to study the course of dysentery. Finally, investigators in the 1920s used prisoners in San Quentin, California to study the effects of implants of testicles taken from executed prisoners and rams.[14]

III. The Disparities between Ethics and Practice.

The research protocols that so flagrantly violated the existing ethical precepts in human experimentation were not carried out covertly or kept hidden from view. To the contrary, the findings were published in the major and widely read medical journals. Nevertheless, the conduct did not incite professional criticism, let alone discipline, except in a handful of cases. To be sure, Osler and several colleagues forcefully condemned some of the protocols described here, including the yellow fever and breast cancer examples. But these were individual reactions and the occasional efforts made to move beyond that to a more official condemnation or censure failed.

Why this professional passivity before these violations of ethics? First, such bodies as the American Medical Association had little authority or organizational standing. Well into the opening decades of the twentieth century, when the profession had managed to impose some standards on medical education and

medical licensing, it still did not yet enjoy sufficient status or cohesion to act in concert in the arena of human experimentation. Second, and closely related to its lower status, the profession was unwilling to draw greater attention to ethical misdeeds for fear of arming its critics, particularly the outspoken members of anti-vivisection societies. To concede that some investigators acted irresponsibly was to give ammunition to those who thought that all investigators acted irresponsibly, and thereby subvert the entire research enterprise. Commenting on a recent discussion in the German parliament on research which purposefully infected prostitutes with syphilis, the *Journal of the American Medical Association* joined in the condemnation of the research but, apprehensive about lay reactions, added: "If laymen would divert their attention to charlatans...the world would be benefited, while these attacks on the regular profession tend to impair the confidence of the public in trained physicians and thus they fall easy prey to unscrupulous quacks."[15] The contention was by no means ill-founded. There was a popular and widespread suspicion about what went on in medical laboratories. Even so, the professional response to the violations was exceptionally timid.

Third, the absence of collective action may reflect the fact that the human subjects put at risk and harmed were almost always marginal to the society. They were poor Southern blacks, or prison inmates, or residents of orphan asylums, themselves vulnerable in all so many ways to abuse but outside the net of public concern. To mount a campaign on their behalf would have been extraordinary, and a reluctance to do so--particularly if it might lower the prestige of medical research--is not altogether surprising. The researchers, in the end, were abusing <u>other</u> people's bodies.

IV. Human Experimentation in the United States, 1940-1945.

The record that we have explored here provides the context for understanding the conduct of human experimentation in the United States during World War Two. The challenges that military needs posed for American medicine were pressing, including how to protect soldiers against malaria, particularly when the Japanese controlled the supply of quinine; how to protect them against influenza, especially in the wake of the 1919 pandemic; and how to protect them against

dysentery. Investigators diligently attempted to develop vaccines or antidotes and to these ends, human experimentation was vital. There were few useful animal models available and to compound the difficulties, malaria was not naturally occurring in the United States, dysentery was rare, and influenza unpredictable. For obvious reasons, the diseases could not be researched where they were found, that is, under battlefield conditions. This meant that researchers had to create the very conditions that they had to study. Put more directly, they had to infect subjects with the disease organisms and test their preparations against them for efficacy.

How did the investigators recruit subjects for their research and were they respectful of the norms of consent and do no harm? In the overwhelming majority of cases, the answer is no. The subjects were typically made up of institutionalized mentally disabled persons (suffering from mental illness or mental retardation), institutionalized orphans, and prisoners. None of them were truly capable of giving consent, certainly not the mentally incompetent or the orphaned children, and (although this point has been debated) not convicts deprived of liberty, living in conditions of severe deprivation, and under total state control. Thus, the researchers violated long-standing ethical norms by carrying out non-therapeutic experiments that were dangerous and lacked subjects' consent.

In specific terms, researchers conducted their studies on dysentery in state institutions for the retarded. Indeed, government research grants favored investigators who had "access to various state institutions where facilities for study of dysentery are unexcelled," precisely because hygienic conditions were so primitive. Researchers also carried out their investigations in orphan asylums; the boys at the Ohio Soldiers and Sailors Orphanage, were injected with "killed suspensions for various types of shigella group of bacteria," to see whether the compounds would protect against dysentery. Unfortunately, the preparations proved highly toxic, causing fevers on the average of 104 degrees and leaving the boys exhausted.

The influenza research used subjects residing in state facilities for the retarded, in correctional centers for juvenile offenders, and in state hospitals for the chronic mentally ill. The protocols divided the residents in two--one group

received the trial vaccine, the other a placebo, and then both were challenged with influenza virus. The vaccines proved to be of varying efficacy, but all the control group and many of the active agent group contracted high fevers and suffered aches, pains, and debilitation.

The bulk of the malaria research went on in state mental hospitals and prisons. In one series of experiments, psychotic, backward patients were infected with malaria through blood transfusions and then given experimental antimalarial therapies. A psychiatrist was a member of the team, but his function was not to determine the subjects' competency to give consent but to explain their symptoms to the investigative team.[16]

Thus, the marked disparity between the principles of research ethics and the reality of laboratory practices prior to the issuance of the Nuremberg Code confirms the import of promulgating a formal code. In its absence, individuals cogently and persuasively defined the rules of conduct that should govern human experimentation, but their precepts lacked formal standing or authority. What was so crucial, then, about the Nuremberg Code was not so much its content as its form. Its authors correctly insisted that the guidelines expressed well known and established values. Its uniqueness lies in the fact that these principles were formally endorsed by a court and presented as a code.

Thus, to understand the history of human experimentation immediately after Nuremberg, it must be remembered that this codification of principles owed little to organized medical bodies. The prosecutors called physicians as witnesses and used them as consultants, but the document stood as the work of judges and its stipulations were realized through a court, not through professional medical bodies. In essence, the initial regulatory effort in human experimentation was external to medicine--which helps to account for both its weaknesses and strengths in the post-World War Two period.

V. The Impact of the Nuremberg Code in the United States, 1947-66.

The externality of the Code to the medical profession helps to explain why Nuremberg exerted so little impact on the conduct of human experimentation in the United States in the immediate aftermath of World War Two.[17] Although the

Code was certainly known to investigators and government officials, references to it in the medical literature were sporadic and occasional. Even more important, investigators themselves paid little heed to the Code's principles. They continued the practices that had marked research during the period 1941-45, carrying out harmful non-therapeutic protocols on subjects incapable of giving consent. Accordingly, researchers transplanted cancer cells into demented old men in order to study the body's immune reactions; they fed hepatitis virus to children in institutions for the retarded to analyze the etiology of the disease and try to create a vaccine. They injected patients with radioactive substances to evaluate the dangers of radioactive fallout to the population in the event of an enemy attack. Each of these experiments violated the opening provision of the Nuremberg Code: "The voluntary consent of the human subject is absolutely essential. This means the person involved should have legal capacity to give consent...and should have sufficient knowledge and comprehension of the elements of the subject matter involved so as to enable him to make an understanding and enlightened decision." But that maxim did not serve as a barrier to the research.

Why should this have been so? Why did Nuremberg have such limited influence? The answer is not that no one had heard of Nuremberg or read its provisions. Rather, the problem goes deeper. Part of the explanation is that the urgency created by World War Two gave way to an urgency created by The War Against Disease and the Cold War. The search for new knowledge seemed (as it always does?) so important as to justify overriding ethical precepts. In part, too, Americans presumed that the Code had no relevance to them, that is, to real scientists trying to advance the well-being of mankind. Nuremberg was written for Nazis, not for physicians--indeed, many Americans believed, altogether mistakenly, that the perpetrators of the gross misdeeds had not been doctors or authentic investigators, but madmen, political hirelings, or "pseudo-scientists," as Andrew Ivy called them.[18] No less important, however was the fact that the Code stemmed from a judicial process. Composed by lawyers, Nuremberg had no medical imprimatur or professional standing. Since it came from outside medicine, it carried no relevance to medicine.

Inseparable from the question of why researchers for two decades ignored

Nuremberg is the issue of defining the ethical standards by which these investigators are rightly judged. The claim is often advanced, usually by physicians but occasionally by others as well, that to fault these investigators for ignoring the principle of consent is to impose the standards of the 1980s on actors and events in the 1950s and '60s, to be guilty of ex post facto reasoning. But the glaring weakness of this contention should already be apparent from the recognition, emphasized above, that the relevant principles went back at least to Bernard and Osler, and truly to Hippocrates. Moreover, by the mid-1960s, Nuremberg was not the only collective judgment on ethical research conduct. In 1946, the Judicial Council of the American Medical Association promulgated a code of research ethics which required "the voluntary consent of the person."[19] In 1964, the World Medical Association published its Declaration of Helsinki, insisting that subjects be informed of the aims, methods, benefits, and hazards of the research before they participated. A defense of "they knew not what they did" surely seems flimsy.

Nevertheless, the debate on the standards for evaluating the ethics of the 1950s and '60s research continues, most recently and prominently in the public attention devoted to the radiation experiments of this period. In 1994, a journalist in New Mexico, Eileen Welsome, identified by name several persons who had been purposefully injected with radioactive substances and her articles stimulated a flurry of media attention and, in short order, a government investigation spearheaded by a presidential task force. With the cooperation of government agencies, most notably the Department of Energy, the task force uncovered an extraordinary number of protocols involving radiation research over the period 1940-1974, including research involving plutonium on ostensibly terminal patients, radioisotope research on children, often mentally disabled, total body irradiation on cancer patients with advanced disease, testes radiation on prisoners, and environmental radiation in various communities.

Courtesy of this investigation, what do we know now that we did not know before? Perhaps the single most important and unexpected finding is just how aware investigators and government officials were of the Nuremberg Code in particular and of the principles of research ethics, including informed consent, in

general. Despite the minimal coverage given to the Code in the public and medical press, the leadership in the Department of Defense (DOD), the Army and the Navy, and the Atomic Energy Commission (AEC) were fully cognizant of its specific provisions and broader implications. In effect, the ethical standards by which to evaluate the conduct of the researchers were the standards that led up to and were encapsulated in the Nuremberg Code.

The AEC as early as 1947 appreciated that to pass ethical review, human experimentation had, in its own words, to carry an expectation of "therapeutic effect," and had to be "susceptible of proof that, prior to treatment, each individual patient, being in an understanding state of mind, was clearly informed of the nature of the treatment, and its possible effects, and expressed his willingness to receive the treatment." Thus, the AEC documents insisted on the competence and "informed consent" (the AEC actually used the term), of the subjects, and ruled out research with no therapeutic benefit.[20]

When the AEC and the DOD were concerned about the risk to air crews posed by nuclear powered engines and considered using prisoners to test effects of exposure levels, one AEC official, Shields Warren, remarked, "It's not very long since we got through trying Germans for doing exactly the same thing;" another investigator, Joseph Hamilton, warned that the proposal "would have a little of the Buchenwald touch." Indeed, many armed services administrators (especially in the Navy) insisted that human experimentation proceed only with consent from subjects and some investigators did respect the principle.[21]

Nevertheless, and once again, the gap between established principle and deed was substantial. The historical record of radiation research is replete with dispiriting examples of administrators failing to implement the ethics they espoused. Thus, the DOD incorporated the Nuremberg Code into its regulations and then, amazingly, classified the document Top Secret and would not even distribute it within its own network. The AEC banned non-therapeutic research, but did nothing to enforce it within its ranks, including its contract research organizations. Whenever agency lawyers issued recommendations about the desirability of legislation to govern the conduct of human experimentation, other agency officials resisted. Some of them, reminiscent of physicians in the early twentieth

century, were fearful of "unfavorable publicity;" others worried that "To commit to writing a policy on human experimentation would focus unnecessary attention on the legal aspects of the subject," and narrow the discretion that researchers' enjoyed.[22]

Perhaps most discouraging, clinical research often sacrificed the well-being of subjects even as researchers and government officials went to great lengths to keep the protocols secret. Thus, Ebb Cade, a 53 year old "colored male," who was hospitalized following an auto accident but otherwise enjoyed good health, was injected, without his knowledge or consent, with 5 micrograms of plutonium at the Oak Ridge Army Hospital as part of a project to study the effects of plutonium on workers. In all, as the presidential task force discovered, "at least twenty-two patients were administered long-lived isotopes in experiments." Nor were these subjects invariably terminally ill, a criterion that in itself is suspect but did carry the rationale of obviating a fear of long-term harmful effects.[23] When the AEC considered the release of some of these research reports, an AEC declassification officer concluded that such a step was unthinkable:

> *The document appears to be most dangerous since it describes experiments performed on human subjects, including the actual injection of plutonium into the body....It is unlikely that these tests were made without the consent of the subjects, but no statement is made to that effect and the coldly scientific manner in which the results are tabulated and discussed would have a very poor effect on the public.*

There was no evidence for the assumption that consent had been obtained and all of the plutonium protocols violated the AEC ban on non-therapeutic research. As the president's task force rightly concluded: "Concerns about adverse public relations and legal liability do not justify deceiving subjects, their families, and the public."[24]

Thus, in the research conducted as part of the Cold War, as with the research conducted in the war against disease, well established ethical principles did not restrain or modify investigators' behavior. It was not that they were ignorant of the standards. But in their quest for knowledge--and for grants, prizes, and fame as well--they transgressed them. Again, the subjects who were kept in ignorance

and put at risk were almost always members of vulnerable groups. In the 1950s and '60s, as in the 1940s, those who suffered the most harm were mentally disabled or prisoners or minorities. And again, those who broke the codes suffered no adverse professional consequences. To the contrary, professional organizations often praised and rewarded them for their work--as though the importance of their findings overrode violations of research ethics.

VI. Imposing Ethics on Human Experimentation: 1966 to the Present.

The critical changes that finally brought ethical standards into the practice of clinical research owe more to an aroused public than a troubled medical profession. Forces external to medicine helped to bridge the persistent and considerable gap that had for so long separated principle from practice. The catalyst was a series of exposés in the 1960s and the early 1970s that made the ethics of human experimentation into headline stories. The behavior of researchers appalled citizens and forced the federal government, specifically, the National Institutes of Health (NIH), to impose new regulations upon clinical research. Put most succinctly, it was scandal that finally brought ethics into the laboratory.

What constitutes a scandal? First, the behavior must be perceived as an offensive to one's moral feelings. Second, it must be committed by someone who is trusted and looked to as an example. Third, it must be making public what had heretofore been a closely guarded secret, known to a small circle of participants but hidden from broader view. In this sense, an ordinary robbery by a thief is a crime, not a scandal. To enter the realm of scandal requires that the perpetrator be someone who has been trusted and the act itself must bring a gasp of surprise and a shudder of revulsion.

It was the 1966 publication by Harvard Medical School professor Henry Beecher, "Ethics and Clinical Research," in the *New England Journal of Medicine*, that cast the record of human experimentation in the mold of scandal. Beecher described in capsule form 22 protocols of "dubious ethicality." He named no names and provided no footnotes; the NEJM had the citations, checked them, and agreed to publish the piece without references. To make certain that the story was not lost--remember that in the 1960s there were few medical journalists and they

did not scrutinize the weekly medical journals as closely as they do now--Beecher alerted the popular press to the article, and his disclosures received sustained attention.

The 22 protocols were shocking to the conscience. They included the hepatitis experiments on the retarded and the cancer cell experiments on demented old men. They also described military research that withheld known agents of efficacy against rheumatic fever, and research at NIH itself that involved new methods of cardiac catheterization. None of the published articles suggested that the subjects had been informed about the experiments; indeed, many of subjects were incapable of giving consent because of their diminished capacity. When Beecher was asked whether the researchers might have obtained consent but neglected to say so in their publications, he aptly responded: "I have worked on the ward of a large hospital for 35 years [and] I know perfectly well that ward patients will not...volunteer for any such use of themselves for experimental purposes when the hazard may be permanent injury or death."[25]

The 22 protocols had appeared in prominent medical journals, including five in the *Journal of Clinical Investigation* and two in the *Journal of the American Medical Association*. They were funded by NIH, by drug companies, and by the armed services, and carried out at major universities, including Harvard and Case Western Reserve. The protocols, in other words, represented mainstream science at mainstream institutions by mainstream investigators--and no one, until then, had criticized the work.[26]

Why was the public so disturbed by the research? After all, the response might have been more calculating and self-serving. The subjects, after all, were marginal to the society (retarded or senile), the research was very important (curing cancer or creating a vaccine against hepatitis), and by strictly utilitarian criteria, the good that would come might outweigh the injuries imposed. But that was not the position adopted. The popular identification was with the subject, not with investigator.

One reason for this special angle of vision, a looking out onto the world from the vantage point of the underdog, was Nuremberg itself, the significance of the crimes committed by the Nazi doctors. The relative silence that surrounded

Nuremberg in the 1950s and early 1960s had finally lifted. Why it took so long for Nuremberg to enter the public consciousness has never been clear--perhaps the events were so traumatic that a kind of psychological repression took hold. But first with the Eichmann trial and then with increasing scholarly and media attention thereafter, the events became a more common reference point. It was no longer possible to justify risks and injuries to human subjects on the grounds that the state required answers to pressing medical questions. Even German medicine, once so prestigious, had been corrupted by succumbing to an ideology that state interests trump other considerations.

If Nuremberg was one foundation for new perspectives toward human experimentation, the second was the social awareness that medical advances affected not only the individual patient but society more generally, and given the dimensions of the potential transformations, research had to be reviewed and authorized by someone other than the single investigator. Transplant procedures were one case in point: should this society promote a medical technology that makes the body into a collection of spare and reusable parts? Moreover, physicians themselves were often eager to share responsibilities in decision-making about outcomes and resource allocation. The most noteworthy example was physicians in Seattle establishing a lay kidney dialysis committee (more popularly known as the "Who Shall Live Committee"), to decide who received the life-saving benefits when the machines were in very short supply. So too, the development of nuclear weapons also encouraged biologists to convene the Asilomar Conference and to delay recombinant DNA research until a broader consensus about its safety was achieved.[27]

Finally, the public reaction was consistent with the sensibilities of the 1960s. This was the decade when the civil rights movement flourished, when most Americans came to view racial discrimination and segregation from the perspective of the disadvantaged minority. When brutish redneck sheriffs threatened peaceful protesters with snarling dogs, Americans identified with the victims, not with the authority figures. And by extension, when investigators took advantage of senility or retardation, Americans identified with the victims, not with the physicians. In all, the 1960s was a moment when the discretionary authority of

parents, husbands, principals, wardens, and mental hospital superintendents lost legitimacy, when the rights of children, women, students, prisoners, and mental patients were advanced. In terms of principles, paternalism declined in appeal and autonomy rose. Inevitably, this reorientation entered medicine, promoting change in the conduct of human experimentation.

The impact of these several considerations was substantial because they were easily and quickly led to structural changes. In the United States, more so than in Europe, the federal government was the primary funder of clinical research. The funds were distributed through the grants made by the NIH, and NIH, in turn, was dependent upon Congressional appropriations. Thus, public disapproval of the conduct of human experimentation came to the attention of Congressmen, who then expressed their displeasure to officials at NIH. These officials were acutely sensitive to Congressional reactions, recognizing that disfavor might reduce or cut off appropriations. At the same time, they had ample authority over grantees--whatever requirements NIH incorporated into its grant awards would be readily accepted. In brief, the fact that NIH was at once subordinate to Congress and superordinate to the investigators meant that exposes would affect policy. Put into the framework that we have been analyzing here, for the first time, the governance of human experimentation moved directly into medicine. In this way and in the wake of scandal, ethics and practice finally came together.

The essential regulatory mechanism was the Institutional Review Board. By federal regulation, all recipients of federal grants must secure IRB approval before conducting research on human subjects.[28] Every grant-receiving institution must establish an IRB, with a membership of no less than five persons, at least one of whom is not be affiliated with the institution. The IRB's mandate is, first, to review clinical research protocols to determine whether the benefits of the proposed research outweigh the risks; second, it must make certain that the investigators have explained all the relevant issues to the subjects and received their informed consent. Although the regulations apply only to federally funded research, many states and the great majority of academic institutions require IRB review for any clinical research performed within their jurisdiction, no matter what the source of funding.

Although IRBs were imposed upon the research community, it is the research community that controls them. To look at the IRB only in terms of its formal structure and organizing principles, it would seem to be a paper tiger. The regulations do not on the whole protect against sloppiness or venality. The power to approve or disapprove research on ethical grounds is granted to a local institutional committee, controlled by members of the same institution that is seeking the funding. It is these insiders that dominate decision making and they are themselves researchers who know that the standards they set for others will come back to affect them as well. Moreover, federal regulations are silent on how the local institution makes appointments to the committee, how long members serve, and on what grounds a member may be dismissed or not reappointed. Hence, it is eminently possible that a member who takes a very hard and uncompromising position on the ethical issues will not be reappointed, and more permissive members will be.

These design features, however, also contribute to the strengths of the IRB. The committee is integral to the institution, its ethical standards incorporated into the ongoing research activities. Since it is colleagues, not outsiders, that make the decisions, a would-be investigator does not want to risk their derision or their rejection. For reasons of self-interest as well as a sensitivity to ethical concerns, they would not dare to propose purposefully infecting retarded inmates of an institution with a virus or radioactive substance, or transplanting cancer cells to senile patients. In the end, the quality of an IRB's work depends inordinately on the conscience and commitment of its members--which is why it appears at once so effective a mechanism to those within a medical institution and so frail a structure to those analyzing it from outside.

Thus, the history of human experimentation makes clear that left to itself, medicine in its collective capacity does not necessarily generate change, even when a sizeable gap separates professed ideals from actual practice. The impetus must come from outside, whether from a court, as with Nuremberg, or from federal regulation, as with the IRB. That said, individual physicians may play a critical role, as witness Andrew Ivy at Nuremberg, and Henry Beecher in the mid-

1960s. Even more important, external forces can generate internal conformity to ethical standards, not as thoroughly as some might wish, but, as the IRB itself demonstrates, more successfully than before.

Still, the reluctance of professional medical bodies to move rapidly and effectively to confront challenges to medical ethics is particularly worrisome in light of the challenges that clinical medicine faces today. The rise of managed care and other forms of corporate provider organizations are putting the ethics of clinical practice to new and hard tests; it is uncertain, for example, whether such fundamental principles as the physician's first and final responsibility to the well-being of the patient can survive in a health care system dedicated to generating profits for shareholders and company officers. Clearly the threat requires energetic and principled response from professional medical bodies. In the terms we have been analyzing here, individual declarations of guiding principles will not suffice now, any more than they did when Claude Bernard or William Osler advanced them. What is needed is an assertion of collective responsibility, not singular expressions of dismay. Whether medicine will prove capable of mounting this effort is the question that will dominate medical ethics and medical care in the coming decades.

ENDNOTES

1. Although Nuremberg was not the very first code on human experimentation promulgated, the two examples usually offered, ironically from Germany (in 1900 and 1931), were so little known as to represent a minor qualification. For a discussion of these codes see Michael A. Grodin, "Historical Origins of the Nuremberg Code," in the book he co-edited with George J. Annas, *The Nazi Doctors and the Nuremberg Code* (New York: Oxford University Press, 1992), 121-44. Some would include the 1946 AMA code, but it was issued very much in response to the Nuremberg trial; see Jay Katz, "The Nuremberg Code and the Nuremberg Trial," *Journal of the American Medical Association*, 276 (1996), 1662-66.

2. Quoted in J.P. Bull, "The Historical Development of Clinical Therapeutic Trials," *Journal of Chronic Diseases*, 10 (1959), 222.

3. For an evaluation of the Nuremberg Code that is, wrongly I believe, dismissive of this history, see Katz, "The Nuremberg Code and the Nuremberg Trial," 1663. Katz insists that "except for occasional voices to the contrary, little thought had been given to patient consent."

4. William Coleman, "The Cognitive Basis of the Discipline: Claude Bernard on Physiology," *Isis*, 76 (1985), 49-70. Although Bernard was most interested in establishing physiology as an autonomous discipline and the laboratory as the site of research, his observations on experimentation went beyond animals to man. And his language describing research was consistently aggressive. Experimental medicine was to "dominate nature," "to conquer living nature. "(pp. 54, 56).

5. *Transactions Cong. Am. Phys. Surg.*, 7 (1907), 1, 7-8.

6. Charles Francis Withington, *The Relation of Hospitals to Medical Education* (Boston: Cupples, Uphman, 1886), 15.

7. See, for example, the discussion in Gerald L. Geison, *The Private Science of Louis Pasteur* (Princeton: Princeton University Press, 1995), ch. 9, on the debates as to when it was appropriate to move from animal experiment to clinical trial.

8. Claude A. Smith, "Uncinariasis in the South, with Special Reference to Mode of Infection," *JAMA*, 43 (1904), 596.

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9. Susan E. Lederer, *Subjected to Science: Human Experimentation in America before the Second World War* (New York: Oxford University Press, 1995), 17, 61.

10. A.A. St. M. Mouritz, "Human Inoculation Experiments in Hawaii including Notes of Arning and of Fitch," condensed, arranged and annotated by W. Wade, *International Journal of Leprosy*, 19 (1951), 205.

11. George M. Sternberg, "The Bacillus Icteroides (Sanarelli) and Bacillus X (Sternberg)," *Transactions of the Association of American Physicians*, 13 (1898), 71 (discussion of paper by Osler).

12. Quoted by Lederer, *Subjected to Science*, 63.

13. "Grafting Cancer in the Human Subject," *JAMA*, 17 (1891), 234.

14. Lederer, *Subjected to Science*, 110-11. For still another experiment on prisoners, this with cholera, see Kristine A. Campbell, "Knots in the Fabric: Richard Pearson Strong and the Bilibid Prison Vaccine Trials, 1905-1906," *Bulletin of the History of Medicine*, 68 (1994), 600-38.

15. "Experiments on Human Beings," *JAMA*, 34 (1900), 1359.

16. For further details of the American wartime research see, David J. Rothman, *Strangers at the Bedside* (New York: Basic Books, 1991), chapter two.

17. For an absence of citations to the code in American law, as well as for a discussion of Bonner v. Moran, "the only *nontherapeutic* experimentation case decided by a U.S. court before the articulation of the Nuremberg Code," see George J. Annas, "The Nuremberg Code in U.S. Courts: Ethics versus Expediency," in Annas and Grodin, *The Nazi Doctors*, 201-222.

18. Andrew Ivy, "Nazi War Crimes of a Medical Nature," *Federation Bulletin*, 33 (1947), 133-46. Ivy himself recognized that only some of the investigators fit this category and that the medical profession itself in Germany had been undermined.

19. *JAMA*, 132 (1946), 1090.

ENDNOTES

20. Advisory Committee on Human Radiation Experiments, *Final Report*, October 1995 (Washington, D.C.: Government Printing Office, 1995), 87.

21. Advisory Committee, *Final Report*, 99.

22. Advisory Committee, *Final Report*, 101, 104.

23. Advisory Committee, *Final Report*, 243.

24. Advisory Committee, *Final Report*, 253, 1255, 269.

25. Quoted in Rothman, *Strangers at the Bedside*, 75.

26. Rothman, *Strangers at the Bedside*, chapter 4.

27. This argument is presented more fully in Harold Edgar and David J. Rothman, "The IRB and Beyond: Future Challenges to the Ethics of Human Experimentation," *The Milbank Quarterly*, (December, 1995). See also, Rothman and Edgar, "New Rules for New Drugs: The Challenge of AIDS to the Regulatory Process," *The Milbank Quarterly*, Volume 68, Supplement 1, 1990

28. 45 Code of Federal Regulations 46.101 et. seq..