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Comments

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Articles

REGULATION OF RESEARCH ON THE DECISIONALLY IMPAIRED: HISTORY AND GAPS IN THE CURRENT REGULATORY SYSTEM

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I. INTRODUCTION

I am honored to have been invited to write the lead article in the inaugural volume of the *Journal of Health Care Law & Policy*. This volume and the conference which inspired it mark critical events in the public conversation about the use of those who are decisionally impaired in research.

The term "decisionally impaired" poses a recurring definitional problem. All of us are going to be decisionally impaired at one time or another. The causes could be many: immaturity, disease, the secondary effects of medication, or disorienting life events, among others. This paper will focus on that kind of decisional impairment that is chronic rather than acute, and is pathological rather than associated with "normal" youth or aging. I readily grant that there can be exceptions to this generalization, but it may help us avoid entering into related but distinct issues and populations, such as decision-making for those in the emergency setting (usually an acute and not

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chronic decisional deficit), or for those who are very young (usually normal and not pathological).

With this rough delimiting framework as a guide, I will attempt to develop an outline of the history and ethics of research regulation with this heterogeneous population. In developing this outline, I encountered an unhappy fact about the scholarship in this area that the present paper is intended to help ameliorate. There is, so far as I can tell, no authoritative history of the use of persons who are decisionally impaired in biomedical and behavioral research, nor is this population commonly identified in the historical literature as distinctly at risk for involvement in a study. This scholarly neglect now shows signs of abating, as does the neglect of this population in the policy arena.

Personal Orientation to Human Subjects Research

While readers with an interest in this topic may be aware of my work on the history and ethics of research with human subjects, they may not realize that my interest in research with those who are decisionally impaired began when I was about 10 years old.¹ My father, J.L. Moreno, was a distinguished psychiatrist who pioneered the fields of group psychotherapy, psychodrama, sociometry, and role playing.² I grew up on the banks of the Hudson River in Beacon, New York, on a 20 acre tract that included a small psychiatric hospital, which my father modeled on the European sanitariums he knew as a medical student in Vienna. My home was about 80 yards from the hospital. Although my parents tried to keep me an appropriate distance from the patients, my earliest friends included persons with schizophrenia, manic-depression, drug addictions, senile dementia, and other neurological disorders.

One day in 1962 a busload of young people arrived on the grounds. They were patients at a local state hospital who were to participate in a special therapy weekend at the Moreno Sanitarium. I remember organizing a softball game after they got settled, and one

1. See generally Jonathan D. Moreno, *Reassessing the Influence of the Nuremberg Code in American Medical Ethics*, 13 J. CONTEMP. HEALTH L. & POL'Y 347 (1997); Ruth Faden et al., *U.S. Medical Researchers, the Nuremberg Doctors Trial and the Nuremberg Code: A Review of the Findings of the Advisory Committee on Human Radiation Experiments*, 276 JAMA 1667 (1996); Jonathan D. Moreno, *Ethical Considerations of Industry-Sponsored Research: The Use of Human Subjects*, 15 J. AM. COLL. NUTR. 35s (1996); Jonathan D. Moreno & Susan Lederer, *Revising the History of Cold War Research Ethics*, 6 KENNEDY INST. ETHICS J. 223 (1996); Jonathan D. Moreno, *The Only Feasible Means: The Pentagon's Ambivalent Relationship with the Nuremberg Code*, 26 HASTINGS CENTER REP. 11 (1996).

2. See generally RENÉ F. MARINEAU, JACOB LEVY MORENO 1889-1974: FATHER OF PSYCODRAMA, SOCIOMETRY, AND GROUP PSYCHOTHERAPY (Dr. Malcolm Pine ed., 1989).

young man remarked that the place seemed pretty good. "Yeah," another fellow replied, "but once they start giving you the stuff, it'll be just like anywhere else." The remark stuck with me, perhaps because I was a little hurt by it, but also because I wondered what "the stuff" was, especially that weekend. My father did not work much with drugs; he was too old-fashioned to accept wholeheartedly the pharmacologic revolution in psychiatry.

Later I learned that "the stuff" in question that weekend was an hallucinogen that later became a symbol of an era, but was unknown to most people at the time. It was lysergic acid diethylamide, LSD-25. The goal was to examine its effect as an adjunct to group psychotherapy. Evidently the results were disappointing. According to my mother, a well-known therapist who also worked with the patients that weekend, it was too hard to tell where the drug left off and the personality began. Neither of my parents took the drug themselves. My father's former Harvard colleague, then Hudson Valley neighbor, Timothy Leary, later proved a more willing guide to the psychedelic world to come.

That weekend on the Hudson I witnessed a gathering for therapeutic research. I have since wondered whether any consent process was involved when the patients were recruited for the LSD-cum-psychotherapy weekend, but since these were state hospital patients in 1962 and a benefit was intended, a consent process worthy of the name seems unlikely. I do know that my father was aware of and troubled by these issues. His compassion for his patients, with whom he identified far more than with his professional colleagues, contributed to his reputation as a maverick. In the memoirs he completed shortly before his death in 1974, he recalled his work as a second year medical student in the clinic of Julius Wagner von Jauregg, an important figure in the history of psychiatric research. The year was probably 1915, and the place was Vienna, Austria, but the culture of academic medicine sounds familiar:

There was no salary for being a research assistant at the clinic, just a tremendous amount of prestige in being there, a wonderful opportunity to meet and to work with some of the top psychiatrists, both research and clinical, in the world, and, in my case, to have my name on publications, still an important factor in a young scientist's career. I was involved in a few other research projects there, but the only one I remember is a study of iodine metabolism. We went to the Tyrol and injected rats full of iodine After experimenting on rats, we experimented on inmates at the psychi-

atric hospital connected with the Von Jauregg clinic, Steinhoff hospital.

I have always been appalled at the idea of experimenting on helpless mental patients. I remember projects — I was not involved with them — in which patients were injected with TB bacilli and another in which injections of alcohol were administered.³

Shortly after the incidents my father recalled, in his graduation year 1917, his mentor Wagner von Jauregg experimented with the induction of fevers as a cure for general paresis, a condition that occurs during the tertiary phase of syphilis and can cause insanity, paralysis, and death.⁴ He injected nine paralyzed patients with malaria, which was subsequently cured with quinine.⁵ The malaria-induced fevers were claimed to cure a large percentage of the patients.⁶ For his discovery, Wagner von Jauregg was awarded the Nobel Prize for Medicine or Physiology in 1927, and malaria therapy for general paresis has since been superseded by penicillin therapy.⁷

Important as it was, Wagner von Jauregg's work was clouded by his questionable use of mentally ill patients as research subjects, a practice which was apparently common in Austrian psychiatry and neurology at the time. Interestingly, Wagner von Jauregg himself was an ardent campaigner for laws to protect the insane from persecution and discrimination.⁸ Physicians in that part of the world must have been well aware of problems in research ethics. In 1892, a Prussian medical school professor had given blood serum from people with syphilis to four children and three young prostitutes.⁹ Dr. Albert Neisser worked on a syphilis vaccine, but failed to ask the permission of those he infected or their legal guardians.¹⁰ When several contracted the disease, newspapers carried banner headlines about the scandal.¹¹

3. J. L. Moreno, *The Autobiography of J. L. Moreno*, M.D. 5-7, 8 (1974) (unpublished manuscript, on file with author) (an abridged version was published in 42 *J. GROUP PSYCHOTHERAPY, PSYCHODRAMA & SOCIOMETRY* 59 (1987)).

4. See Julius Wilson von Jauregg, *NOBEL PRIZE WINNERS: AN H.W. WILSON BIOGRAPHICAL DICTIONARY* 1092, 1093 (Tyler Wasson ed., The H.W. Wilson Co., 1987).

5. See *id.* at 1093.

6. See *id.*

7. See *id.*

8. See *id.*

9. See Michael A. Grodin, *Historical Origins of the Nuremberg Code, THE NAZI DOCTORS AND THE NUREMBERG CODE* 121, 127 (George J. Annas & Michael A. Grodin eds., 1992).

10. See *id.*

11. See *id.* at 128.

In 1900, the Prussian government directed that medical research must have the human subject's consent.¹²

II. RESEARCH WITH SICK PATIENTS

Historically, experiments with sick patients afflicted with the disease being studied have not been perceived as bound by the same ethical constraints as research with healthy, "normal" subjects. This long-standing perception has also been examined in another context by the Federal Advisory Committee on Human Radiation Experiments, which reported to President Clinton in October 1995 on government-sponsored studies of ionizing radiation.¹³ If this reconstruction of an historical assumption is correct (an assumption of which people may not of course have been aware at the time), it may help to explain why certain very public experimental uses of the decisionally impaired rarely provoked a general outrage: They were assumed to fall within the then-privileged domain of doctor-patient relationships.

The only other Nobelist in psychiatry, Portuguese physician Egas Moniz, who won in 1949 for Physiology or Medicine, also engaged in experiments with sick patients.¹⁴ "American physiologists had experimented with monkeys by surgically removing their prefrontal lobes."¹⁵ As a result, the monkeys no longer became upset when they made mistakes carrying out complex tasks they had learned; they seemed to be immune to anxiety and frustration.¹⁶ Moniz theorized that the same may be true for severely anxious or aggressive mental patients.¹⁷ The operation did seem to cure at least some of the first twenty on whom it was tried.¹⁸ Moniz was forced to supervise the performance of more than 100 "leucotomies" (later called lobotomies) because he was too impaired by gout in his hands to perform the procedure himself.¹⁹ The technique was eventually banned by the Portuguese govern-

12. *See id.* at 127.

13. *Id.*

14. *See* Biography of Egas Moniz, NOBEL PRIZE WINNERS 722, 723-24. (Tyler Wasson ed., 1987).

15. *Id.* at 723.

16. *See id.*

17. *See id.*

18. *See id.* at 724 (noting that of the first twenty operations, seven of the patients were considered cured, eight improved, and five were unchanged).

19. *Id.* (explaining that Moniz dubbed the procedure a "leucotomy," from the Greek word for white, because of the white matter connecting the prefrontal lobes to other parts of the brain that were surgically removed).

ment, but others adopted and widely used lobotomy procedures, especially in the United States.²⁰

Several more innovative somatic therapies were introduced into psychiatry in the 1930s. "Shock therapy" involves electrical impulses or drugs, such as insulin, to induce hypoglycemia, or metrazol to induce convulsions. Contemporary psychiatrists were discomfited by the rush of these new and unproven drastic interventions. As historian Gerald Grob stated, physicians asked whether they should "deploy experimental therapies on patients whose illness often impaired their mental faculties?"²¹ Finally, the pressure to find an effective treatment for the large number of chronic mental patients crowding hospitals in this era of institutionalization overwhelmed such abstract questions. In Grob's words, "[i]f there was even a remote chance that an experimental therapy would aid them, should they be deprived of its use until more conclusive evidence was available?"²² In the history of research ethics, this argument is a familiar, and to some degree, compelling rationale.

The iconic status of the Nobel Prize serves to highlight the complex ethical issues at the heart of the only two Nobels given in psychiatry.²³ But the centrality of these issues in our cultural history extends well beyond these examples. They are embedded in the development of modern, liberal democratic society itself, and in the context of public policy toward the mentally ill. One of the signal events of the French Revolution was the freeing of the inmates of the asylum of Salpetriere by Philippe Pinel who believed, consistent with the revolutionary philosophy, that insanity would be cured by the establishment of a new civil society.²⁴ Some trace to this incident the beginning of the moral treatment movement that dominated the care of the mentally ill for a hundred years, evolving finally into the mental hygiene movement of the early twentieth century.²⁵ Alexis de Tocqueville, one of the most renowned commentators on the American scene, arrived specifically to report on the way the new country was managing its most marginal citizens in new asylums.²⁶ Moral treatment institutions were carefully designed to provide "lunatics" with the social and

20. *See id.*

21. GERALD GROB, *THE MAD AMONG US* 181 (1994).

22. *Id.*

23. I am indebted to my SUNY colleague, Dinko Podrug, M.D., for this point.

24. *See* Jonathan D. Moreno, *The Continuity of Madness: Pragmatic Naturalism and Mental Health in America*, in *CONCEPTS OF HEALTH AND DISEASE: INTERDISCIPLINARY PERSPECTIVES* 645-46 (Arthur Caplan et al. eds., 1981).

25. *See id.*

26. *See id.* at 645.

physical orderliness that might imprint itself on their disordered brains.²⁷ The moral treatment movement was a grand and well-meaning, albeit unsystematic, social experiment with the seemingly recalcitrant problem of mental illness.²⁸

Other innovations in the eighteenth and nineteenth centuries more closely resembled therapeutic research because they were directed specifically toward mentally ill patients.²⁹ Some of these techniques were practiced in moral treatment institutions in spite of their apparent philosophical inconsistency.³⁰ Bloodletting, purging with emetics, and shock therapy all had their day;³¹ had controlled research methods been available, that day would probably have been shorter in every case. When the resources of the new biologically-based medicine combined with randomized controlled trials, a powerful new weapon was theoretically available to psychiatry and neurology as to other disciplines. But until the mid-twentieth century, there remained a frustrating lack of potential drug therapies. Controlled studies of cognitively and socially-oriented interventions, like psychoanalysis and psychotherapy, are notoriously difficult to perform with reliability because of the countless variables that affect these processes.

Finally, in the early 1950s, there was hope for the long sought medical treatment of mental disorders. A class of tranquilizers gained notoriety for ameliorating the symptoms of schizophrenia.³² But here, too, the human research issue casts a shadow. The neuroleptic drugs unquestionably inaugurated a new era in the treatment of the mentally ill, and by the mid-1970s the de-institutionalization policy they helped justify was well-established. Unfortunately, the new "psychoactive" medications also had serious side-effects with long-term use, a fact that was recognized by the 1960s.³³ Some commentators charged that the drug company that marketed Thorazine, the first of these medications, conducted hasty clinical trials in its rush to bring the potentially lucrative new product to market.³⁴ These charges followed the thalidomide tragedy that resulted in the subsequent expan-

27. *See id.* at 649.

28. Similar charges have been lodged against a more recent policy response to mental illness, that is, de-institutionalization. Like moral treatment, de-institutionalization was a large-scale social experiment which did not meet the statutory definition of research.

29. *See* Moreno, *supra* note 24, at 650.

30. *See id.*

31. *See id.* at 648.

32. *See, e.g.*, PHIL BROWN, TRANSFER OF CARE 150-51 (1985).

33. *See id.*

34. *See id.*

sion of the U.S. Food and Drug Administration's (FDA) authority, to include efficacy as well as toxicity in approving the sale of drugs.³⁵ In the case of Thorazine, like thalidomide, the problem was not conducting overly aggressive clinical research, but just the opposite (though thalidomide's teratogenicity was so statistically infrequent that only a massive, large-scale study would have uncovered it). The alleged result was the wide prescription of a psychiatric medication whose long-term effects were not well understood, and which justified a drastically altered social policy, and in effect ignited another social experiment, directed at the perennial problem of mental illness.

III. THE DECISIONALLY IMPAIRED AND NON-THERAPEUTIC RESEARCH

Not all instances of ethically questionable research practices involving those who are decisionally impaired are intended to benefit the subjects, nor are they intended to yield knowledge of the sources of the impairment that affect the subject population. Rather, they may have an entirely unrelated purpose, such as determining the effects of an agent on the human body, or the body's effect on the agent. In these cases the decisionally impaired subject is chosen for research because he or she is readily available, especially if the subject is institutionalized. Two prominent illustrations of this scenario occurred during the 1950s, though they were generally known only much later.

In 1952, Harold Blauer was 42 years old and a jet-setting tennis pro at Manhattan's Hudson River Club.³⁶ Sometime that summer Blauer divorced from his wife and became, in the fall, a patient of Bellevue Hospital.³⁷ He was diagnosed with clinical depression and was admitted voluntarily to the New York State Psychiatric Institute (NYPI).³⁸ Blauer was not aware that the NYPI had a secret contract with the Army Chemical Corps to conduct research using a mescaline derivative.³⁹ In mid-January of 1953, Blauer was given a number of injections with widely varying doses, of which the last one was significantly larger than the first.⁴⁰ Blauer went into convulsions and died

35. See Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355 (1997).

36. See *Barrett v. U.S.*, 660 F.Supp. 1291, 1317 (S.D.N.Y. 1987).

37. See *id.* at 1298, 1317.

38. See *id.* at 1298.

39. See *id.* at 1299. (Blauer was aware that the drugs he was given were "experimental" in the sense that they did not come off the shelf from a pharmacy; however, the primary purpose of the experiment was to gather data that the Chemical Corps required for its investigation of the mescaline derivatives as potential chemical warfare agents).

40. See *id.* at 1296, 1299-1300.

hours later.⁴¹ The Army and New York State arranged a cover-up of the actual circumstances of Blauer's death and split an \$18,000⁴² payment between his widow and two young children. Twenty years later, in 1975, the Secretary of the Army contacted Blauer's daughters about a press release identifying the Army's involvement in their father's death.⁴³ Finally, in 1987, a court awarded Blauer's daughters \$702,044 in compensation from the federal government.⁴⁴

At around the same time that the Blauer case began in the early 1950s, the Atomic Energy Commission (AEC) was helping to support studies that would demonstrate the peaceful uses of nuclear energy.⁴⁵ In one such episode that came fully to light only a few years ago, the AEC co-sponsored with the Quaker Oats company a study of mineral intake in the human body, using as a tracer minute amounts of radiation in breakfast cereal.⁴⁶ Research subjects included emotionally disturbed adolescent boys in Massachusetts institutions known as Fernald and Wrentham.⁴⁷ At Fernald, about which more is known than Wrentham, parents were asked to consent for their boys' participation in a special program called the "science club."⁴⁸ They were not told the true purpose of the club, nor that they would be ingesting tiny amounts of radiation.⁴⁹ In its 1995 Final Report to the President, the Advisory Committee on Human Radiation Experiments found that government officials and biomedical professionals even *at that time* "should have recognized that when research offers *no prospect* of medical benefit, whether subjects are healthy or sick, research should not proceed without the person's consent."⁵⁰

Both the Blauer and Fernald-Wrentham cases involved decisionally impaired subjects. The experiments were neither intended to benefit the subjects nor intended to address the conditions that caused their impairments. Interestingly, both were also projects that were at least partly sponsored by national security agencies, a sector of government that used mental patients in research during the Second

41. *See id.* at 1300.

42. *See id.* at 1305-06. The court issued findings of fact and conclusions of law that stated that Blauer had died as a result of New York State's negligence. *Id.* at 1306.

43. *See id.* at 1306. Blauer's eldest daughter filed an administrative claim with the Department of the Army for wrongful death of her father. *Id.* She filed action in federal court in 1976. *Id.*

44. *See id.* at 1323.

45. *See* Grodin, *supra* note 9, at 172.

46. *See id.* at 196.

47. *See id.* at 210.

48. *See id.*

49. *See id.*

50. *See id.* at 504 (emphasis in original).

World War.⁵¹ The vast majority of wartime subjects were military personnel (mainly in mustard gas studies), conscientious objectors, or prisoners.⁵² Psychotic patients were used in a malaria study, and retarded subjects participated in dysentery vaccine experiments sponsored by the Committee on Medical Research, an arm of the Executive Office of the President.⁵³

Within the pantheon of more commonly-cited research ethics scandals, there is one that also falls into the category of research with the decisionally impaired that is neither intended to benefit them directly nor to contribute to knowledge about the condition that has caused their decisional impairment. In the infamous Brooklyn Jewish Chronic Disease Hospital case in 1963, debilitated patients were injected with live cancer cells, apparently without their knowledge.⁵⁴ The study's purpose was to gather information on how the systems of patients with non-cancerous chronic conditions would respond to the presence of transplanted cells.⁵⁵ The investigators claimed to have obtained verbal consent, of some sort, from the subjects, and defended the lack of documentation on the grounds that more dangerous procedures were performed than this one without consent forms, and they did not want to frighten the patients.⁵⁶ When complaints were filed, state regulatory agencies responded with unusual vigor, and the principle investigator was censured by the New York State Board of Regents, which at that time was responsible for physician certification in the state.⁵⁷

IV. HISTORIC REGULATORY EFFORTS

Most efforts to regulate the use of human subjects have been stimulated by concerns for children in research, likewise, but to a lesser extent for pregnant women and fetuses, and later, prisoners. Nonetheless, prior to the 1970s there were some widely scattered attempts to apply guidelines to the experimental use of the decisionally impaired. One of these occurred in Weimar, Germany. In 1930, a Jewish doctor named Julius Moses reported that 75 children had died in Lubeck as a result of pediatricians' experiments with a tuberculosis

51. See DAVID H. ROTHMAN, *STRANGERS AT THE BEDSIDE: A HISTORY OF HOW LAW AND BIOETHICS TRANSFORMED MEDICAL DECISION MAKING* 30 (1991).

52. See *id.*

53. See *id.* at 34-36.

54. See RUTH R. FADEN & THOMAS L. BEAUCHAMP, *A HISTORY AND THEORY OF INFORMED CONSENT* 161 (1986).

55. See *id.*

56. See *id.*

57. See JAY KATZ, *EXPERIMENTATION WITH HUMAN BEINGS* 9-65 (1972).

vaccine.⁵⁸ The German press was highly critical of the powerful chemical manufacturers for using hospitals to test their new products.⁵⁹ The scandal in Lubeck gave substance to the accusations that people were being exploited for potential profits.

It happened that Moses was also a member of the German Parliament from the Social Democratic Party.⁶⁰ In 1931, he played a key role in pressuring the Interior Ministry to respond to the Lubeck scandal.⁶¹ The resulting rules were far more comprehensive and sophisticated than anything introduced by any government until then, and compare quite favorably with modern regulations.⁶² They included a requirement for consent from informed human subjects.⁶³ Like so much progressive government in the ill-fated Weimar Republic, these regulations were trampled by Hitler's regime, which used tens of thousands of concentration camp inmates in vicious experiments.⁶⁴ After the war, at the Nuremberg trial of the Nazi doctors in 1947, the prosecution team alleged the use of the Interior Ministry guidelines as evidence that these prior standards should have governed the actions of the Hitler regime in the use of human experimental subjects.⁶⁵ As a counter-argument, the legal status of the 1931 guidelines was questioned because they were not cited by the international organization which monitored public health laws and regulations in the 1930s and 1940s.⁶⁶

The team that investigated the Nazi crimes took notice of the abuse of the mentally ill in the context of the "T-4" or "euthanasia" program⁶⁷ that led to the extermination of many psychiatric patients and was, in effect, a rehearsal for the mass murders in the concentration camps. The chief medical advisor to the Nuremberg judges, Leo Alexander, made the Nuremberg prosecutions possible by unraveling

58. See Grodin, *supra* note 9, at 129.

59. See *id.*

60. See *id.*

61. See *id.*

62. See *id.* at 130-31.

63. See *id.*

64. See *id.* at 132.

65. See *id.* at 129.

66. See *id.*

67. Robert N. Proctor, *Nazi Doctors, Racial Medicine, and Human Experimentation*, in *THE NAZI DOCTORS AND THE NUREMBERG CODE* 23-24 (George J. Annas & Michael A. Grodin, eds., 1992). The euthanasia program was planned and administered by the leaders of the German medical community after an October 1939 order issued from Hitler. *Id.* at 23. The order required that certain doctors be commissioned to grant a "mercy death" to patients judged "incurably sick by medical examination." *Id.* The gassing of the mentally ill was a rehearsal for the subsequent destruction of other "lives not worth living," (*e.g.*, Jews, Homosexuals, Communists, Gypsies, and prisoners of war). *Id.* at 23-24.

the horrific story of the camp experiments⁶⁸ from the records of SS chief Heinrich Himmler. Near the end of the trial, Alexander wrote a memorandum to the judges, portions of which were incorporated into the famous Nuremberg Code.⁶⁹ His memorandum became a part of the judges' decision that was their attempt to establish rules to guide human experimentation.⁷⁰ He also singled out the mentally ill as a population that should be given special protections.⁷¹ The judges deleted this reference in their final draft. A likely explanation is that the judges did not want to appear to be interfering in legitimate medical judgments about innovative treatment, but only to rule out non-beneficial and highly risky experiments with easily coerced populations of healthy subjects such as prisoners. Even so, much confusion about the judges' intentions has been caused by the Nuremberg Code's celebrated first line, that "the voluntary consent of the human subject is absolutely essential,"⁷² a formulation that seems to rule out research with children, with emergency patients, and with the decisionally impaired.

When the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Commission) was created in 1974, in the wake of the Tuskegee Syphilis Study scandal, the decisionally impaired were not high on the list of special populations for consideration. The Commission's report on those "institutionalized as mentally infirm" (IMI) came at the very end of their tenure in 1978.⁷³ Moreover, in framing the topic in terms of institutionalized persons, the report seemed to be obsolete. Movements toward de-institutionalization were already well under way in many states, if not largely completed. The coercive aspects of institutionalization were familiar to the Commission from its lengthy deliberations on prison research, but this circumstance failed to capture the more subtle issues of study participation for persons who were no longer likely to be incarcerated in "total institutions."

68. See Grodin, *supra* note 9, at 139.

69. See Proctor, *supra* note 67; see also U.S. DEP'T OF ENERGY, OFF. OF HEALTH AND ENVIRONMENTAL RESEARCH, HUMAN SUBJECTS RESEARCH HANDBOOK SECOND EDITION: APPENDIX - THE NUREMBERG CODE 15-3 to -4 (1993), reprinted from 2 TRIALS OF WAR CRIMINAL BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10, 191-82 (1949).

70. See Grodin, *supra* note 9, at 135.

71. See *id.*

72. See The Nuremberg Code, *supra* note 69, at 15-3.

73. See NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, REPORT AND RECOMMENDATIONS: RESEARCH INVOLVING THOSE INSTITUTIONALIZED AS MENTALLY INFIRM (DHEW Pub. No. (OS) 78-0006, 1978).

On its own terms, the Commission's recommendations called for evaluating research with each class of IMI, including the mentally ill.⁷⁴ The Commission found it advisable, in many instances, to make use of a disinterested third party to ensure that the research is not harmful.⁷⁵ This individual might also play the role of a consent auditor, one who monitors the informed consent process itself and determines whether the potential subject has given a truly competent consent.⁷⁶ Tracking the framework used in its pediatric recommendations, the Commission also urged that persons with diminished capacity be allowed to "assent" to research participation, after which their legally authorized representative must be asked to consent on the subject's behalf.⁷⁷

There is remarkably little literature on the process that led to the rejection of the Commission's recommendations on those institutionalized as mentally infirm in the early 1980s, although they were the least influential portion of the Commission's legacy. According to one former Commission member and prominent bioethicist, Al Jonsen, officials at the National Institute of Mental Health (NIMH) and the Agency for Drug Addiction and Mental Health Association (ADAMHA) objected that the recommendations would stifle important research with their populations.⁷⁸ The reaction of the relevant professional community may perhaps be gauged from a paper published by a consultant to the National Commission, Harvard professor Neil Chayet, who argued in 1976 that the perspectives of law and medicine on informed consent are "fundamentally incompatible — particularly in the area of the mentally disabled, where appreciation of the concept of informed consent is well on its way to paralyzing research and treatment."⁷⁹

With the significant exception of the IMI recommendations, the 1981 Department of Health and Human Services (DHHS) rules largely followed the Commission's work. In 1991, the rules were codified for 17 federal agencies that conduct or sponsor research with human subjects and are now known as the "Common Rule."⁸⁰ The regulations authorize institutional review boards (IRBs) to institute additional safeguards for research involving vulnerable groups, in-

74. See Protection of Human Subjects, 43 Fed. Reg. 11,328, 11,330 (1978).

75. See *id.* at 11,332.

76. See *id.*

77. *Id.* at 11,332.

78. Interview with Al Jonsen, Former Member of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (May 19, 1997).

79. Neil Chayet, *Informed Consent of the Mentally Disabled: A Failing Fiction*, 6 PSYCHIATRIC ANNALS 82-89 (1976).

80. Protection of Human Subjects, 45 C.F.R. §§ 46.101-409 (1997).

cluding the mentally disabled.⁸¹ The safeguards could involve consultation with specialists concerning the risks and benefits of a procedure for these populations, or special monitoring of consent processes to ensure voluntariness.⁸² But it is not known how frequently IRBs actually implement such further conditions.

V. THE CONTEMPORARY DEBATE

There is strong indirect evidence that IRBs are unlikely to compensate for the lack of specific regulations for research with the cognitively impaired by aggressive use of their discretionary authority. Observers of the local review process agree that, if anything, the IRB workload has greatly increased since the 1981 regulations were first implemented.⁸³ IRBs appear to have all they can handle to keep up with their paperwork, as privately funded research has proliferated. Monitoring of a protocol's progress by IRBs after approval is practically non-existent, apart from investigators' routine filing of annual progress reports.⁸⁴ After the initial stages, the direct impact on actual research practices of local review is minimal.⁸⁵

The lack of specific federal guidance on research with the decisionally impaired has also meant that non-federally funded research has gone its own way, or rather at least 50 different ways. The states are a crazy quilt of regulation in this area, with most having no rules that clearly apply to this group while some are quite restrictive.⁸⁶ Recent events in the state of New York illustrate the situation. A state court has prohibited all state-sponsored greater-than-minimal-risk research with mental patients that does not hold potential benefit to the subjects.⁸⁷ The decision in *T.D. v. New York State Office of Mental Health*, resulting from a suit brought by former patients-subjects and several advocacy organizations, came with harsh criticism of state prac-

81. See § 46.109.

82. See § 46.109(e).

83. See, e.g., U.S. GEN. ACCT. OFF., REPORT TO THE RANKING MINORITY MEMBER, COMMITTEE ON GOVERNMENTAL AFFAIRS, U.S. SENATE, SCIENTIFIC RESEARCH: CONTINUED VIGILANCE CRITICAL TO PROTECTING HUMAN SUBJECTS at 17 (U.S. Gen. Acct. Off. 1996).

84. See *id.* at 10.

85. See *id.* at 11.

86. Diane Hoffmann and Jack Schwartz, *Proxy Consent to Participation of the Decisionally Impaired in Medical Research - Maryland's Policy Initiative*, 1 J. HEALTH CARE L. & POL'Y 136 (1998).

87. See *T.D. v. New York State Office of Mental Health*, 650 N.Y.S.2d 173, 193-94 (N.Y. App. Div. 1996), *appeal dismissed by* 680 N.E.2d. (N.Y. 1997); *leave to appeal granted by* 684 N.E.2d 281 (N.Y. 1997); and *appeal dismissed by* 1997 WL 785461 (N.Y. Dec. 22, 1997).

tices, some administrative, some technical, and some constitutional in nature.⁸⁸

It would be ironic if the lack of specific federal guidance resulted in even greater restrictions on research with the decisionally impaired than the National Commission contemplated. The Commission's recommendations were virtually silent about what constitutes "benefit" to the subject, and what little was said about giving notice to subjects or permitting them to appeal research participation would not have satisfied the court in *T.D.*⁸⁹

The growing interest in research with the decisionally impaired stems partly from the most recent well-publicized incident with this population, the suicide of a former subject in a "drug free" or "wash-out" study at the University of California, at Los Angeles (UCLA).⁹⁰ Commentaries on this case and its implications often omit that the subject was two years out of the drug free period of the study and one year out of observation from the study itself.⁹¹ Further, the National Institutes of Health Office for Protection from Research Risks concluded that the study was ethical, but the informed consent form flawed.⁹² Defenders of the research also claim that patients, following admission to inpatient units, are often taken off all medication to establish a baseline, but withdrawing psychiatric drugs poses the danger of relapse and must be carefully managed.⁹³

Several years after the controversy, how should the UCLA study be assessed? Often familiar accounts of ethics cases exaggerate the harms and wrongs done, or the certainty that harms and wrongs were done. For example, the Willowbrook hepatitis studies, although they were ethically flawed, were more complicated in their ethical implications than is often appreciated.⁹⁴ Similarly, as a former staff member

88. *T.D.*, 650 N.Y.S.2d at 184-94.

89. See *supra* notes 73-77 and accompanying text.

90. See Adil E. Shamoo & Timothy J. Keay, *Ethical Concerns about Relapse Studies*, 5 CAMBRIDGE Q. OF HEALTHCARE ETHICS 373-86 (1996).

91. See, e.g., *id.*

92. See OFFICE FOR PROTECTION FROM RESEARCH RISKS DIVISION OF HUMAN SUBJECT PROTECTION, EVALUATION OF HUMAN SUBJECT PROTECTIONS IN SCHIZOPHRENIA RESEARCH CONDUCTED BY THE UNIVERSITY OF CALIFORNIA, LOS ANGELES (1994).

93. See generally Ross J. Baldessarini, *Chemotherapy*, in HARV. GUIDE TO MODERN PSYCHIATRY 387-432 (A. M. Nicolai ed., 1978).

94. See HENRY BEECHER, RESEARCH AND THE INDIVIDUAL: HUMAN STUDIES 119, 122-27 (1970). The Willowbrook study was "directed toward determining the period of infectivity of infectious hepatitis. Artificial induction of hepatitis was carried out in an institution for mentally defective children (many of whom were [five] to [eight] years old) in which a mild form of hepatitis was endemic. The parents gave consent for the intramuscular injection or oral administration of the virus, but little is said as to whether they were informed of the hazards involved." *Id.* at 123.

of the President's Advisory Committee on Human Radiation Experiments, I have been surprised how often someone tells me how awful a certain radiation study was, when the Committee had concluded that the case was far less terrible, or not clearly wrong, as compared to some others. Nonetheless, the UCLA case does point to some problems, though not necessarily those that have attracted most of the attention. For example, how routine are drug holidays? Do studies that require a drug-free period simply "piggy back" on a common practice, or could the desire to enroll patients in studies determine the nature of their care? What merit is there to the theory that there is a "kindling" effect from repeated symptomatic episodes, so that subsequent psychotic states are exacerbated by previous ones? When provocation studies are conducted, should the return of symptoms associated with schizophrenia be evaluated as an inherent harm to be weighed against the potential for direct benefit to the patient?

It is common place that the evolution of research ethics, and especially regulatory changes, is driven by scandal. The lack of guidance to IRBs in the current regulations and the flaws and inconsistencies in state laws would not, perhaps, have come to public attention had it not been for the *T.D.* case⁹⁵ which, if it does not rise to the level of scandal, has at least been a significant source of embarrassment and frustration to the New York psychiatric community. Accordingly, when President Clinton appointed the National Bioethics Advisory Commission (NBAC) in 1995, he included the review of current human subjects regulations in its mandate.⁹⁶ One population in which NBAC is especially interested is the decisionally impaired.⁹⁷

It remains to be seen how the psychiatric and substance abuse treatment communities will react to any new recommendations that emerge from NBAC. It seems likely that whatever is brought forward will be perceived as more restrictive than the status quo, in that it will specify conditions for research with the decisionally impaired. However, psychiatric research has changed a great deal in the past fifteen years. Those who conduct pharmacologic and biologic research are more accustomed to regulation than were those who performed behavioral research twenty years ago, and the former are now dominant in psychiatry.

95. See *supra* notes 87-88 and accompanying text.

96. Exec. Order No. 12,975, 60 Fed. Reg. 52,063 (1995).

97. See generally Meeting of the National Bioethics Advisory Committee (Oct. 4, 1996) (unpublished transcript, portions of which on file with the *Journal of Health Care Law & Policy*).

VI. TOWARD REGULATORY REFORM

There may be few instances of actual abuse in contemporary research involving those who are decisionally impaired. Unfortunately, there is no systematic study of this question. What is clear is that many, but by no means all, advocates for this group believe that more specific rules are needed. However, they are also loathe to impose restrictions that would significantly retard medical progress.⁹⁸ As Alexander Capron has recently written, "no type of research raises more problems than research with the mentally impaired, particularly those who are institutionalized for treatment."⁹⁹ Yet, among populations that are often regarded as "vulnerable" and in need of special protection, persons who are decisionally impaired stand out as potential subjects for whom no regulations have been tailored.

In general terms, there have been many changes in the medical research environment since the 1981 enactment of the DHHS regulations¹⁰⁰ that in 1991 were codified as the "Common Rule" for 17 federal agencies.¹⁰¹ Among the most important of these changes are the increase in multi-site studies and the increasing proportion of privately funded research.¹⁰² As a result, IRBs are faced with challenges not contemplated two decades ago.¹⁰³ They are often in an awkward position with regard to changes in consent forms for important and lucrative multi-site studies, and they are ill-equipped to monitor their colleagues' potential conflicts of interest in contract research.¹⁰⁴ The increasing workload for IRBs has not been accompanied by increased resources for their support, and, as presently structured, the OPRR has little discretion to alter regulatory requirements and encourage a more activist role for IRBs while relieving them of some paperwork that could be handled by qualified staff.¹⁰⁵ Finally, there is growing Congressional concern about research that does not come under federal informed consent requirements, either because it is privately

98. See Alexander M. Capron, *Incapacitated Research*, 27 HASTINGS CENTER REP. 25-7 (1997).

99. *Id.* at 25.

100. See Protection of Human Subjects, 56 Fed. Reg. 28,002 (1991).

101. See Protection of Human Subjects, 45 C.F.R. §§ 46.101-404 (1991).

102. See generally U.S. GEN. ACCT. OFF., REPORT TO THE RANKING MINORITY MEMBER, COMMITTEE ON GOVERNMENTAL AFFAIRS, U.S. SENATE, SCIENTIFIC RESEARCH: CONTINUED VIGILANCE CRITICAL TO PROTECTING HUMAN SUBJECTS, GAO/HEHS Doc. No. 96-72 (1996).

103. See *id.*

104. See *id.* at 8.

105. See *id.* at 17, 19.

funded or because the sponsors do not plan to pursue FDA approval for a drug or device.¹⁰⁶

This litany of general comments about likely areas of continued discussion applies, of course, to research with those who are decisionally impaired as well. But there are a number of more specific items concerning this population. Each of them could be a discussion in itself.

First, a lively debate is beginning about the suitability and practicality of advance research directives for those who are able to anticipate a substantial period of decisional impairment. These directives may be procedural (durable powers-of-attorney for health care) or substantive (specifying what unapproved treatment may be attempted and under what circumstances), but they may be limited by at least two factors, current state laws and practicality.¹⁰⁷

Second, if advance research directives are found to be ethically and legally acceptable and practical, it will need to be determined whether interventions not intended to benefit the patient, or those bearing more than a minor risk, may be authorized in advance by the potential subject. As Rebecca Dresser and Peter Whitehouse have recently argued, "determining an acceptable balance of risks and potential benefits is *the most important ethical challenge in emergency and nonemergency research involving decisionally incapable subjects.*"¹⁰⁸

Third, the National Commission's earlier suggestion about utilizing "consent auditors"¹⁰⁹ during the recruitment of decisionally impaired potential subjects may have renewed prospects. Not only would this system provide another layer of accountability with a disinterested third party, but if required for certain kinds of research, it would serve to encourage IRBs to do more active monitoring of consent processes. Consent auditors may also contribute to the education of investigators and their team members with regard to the conditions for a valid consent.

Fourth, the medical community is going to have to accept the need to subject certain popular study designs to greater scrutiny. "Washout" studies are a prime example, both because of the direct

106. See HHS Oversight Biomedical Ethics: Hearings Before the Subcomm. on Human Resources of the House Comm. On Government Reform and Oversight, 105th Cong., 1997 WL 10570903, (statement of David Satcher, M.D., Ph.D., Director, CDC).

107. See Jason H. T. Karlawish & Greg A. Sachs, *Research on the Cognitively Impaired: Lessons and Warnings from the Emergency Research Debate*, 45 J. AM. GERIATR. SOC. 474, 475 (1997).

108. Rebecca Dresser & Peter Whitehouse, *Emergency Research and Research Involving Subjects with Cognitive Impairment: Ethical Connections and Contrasts*, 45 J. AM. GERIATR. SOC. 521, 522 (1997) (emphasis added).

109. See *supra* notes 74-77 and accompanying text.

harm that is done to subjects by the return of symptoms, and the indirect harm that may be associated with burdensome procedures conducted during the drug-free period, such as the use of neurological imaging devices that can entail discomfort and distress.¹¹⁰ It may still be possible to conduct such studies by making certain modifications, such as beginning a trial with the most moderately affected patients.¹¹¹

Fifth, notice of entrance into a study, as was mentioned previously, should be required regardless of capacity with an appeals process built into the system. As the Maryland Working Group has suggested in its draft legislative proposal, *prima facie* dissent by the subject, regardless of capacity, in the future must be clearly identified as an absolute bar to further participation.¹¹² A related but more difficult question is whether periodic "re-consenting" should be required for certain subjects at certain times in the study, including those subjects whose conditions may render them especially compliant due to dependency.¹¹³

Finally, the FDA's "narrow exception" to the informed consent requirement for emergency research¹¹⁴ may someday be used to justify consent waivers for non-emergency research that is hypothesized to present a very favorable risk-benefit ratio. This movement will begin with those whose decisional impairment is acute and who can be retrospectively "consented" within hours or perhaps days of the intervention. Attempts will then be made to extend the exception to those whose decisional impairment is chronic and whose capacity to consent is a distant possibility. It is not too early to consider whether any system can adequately protect subjects from inappropriate applications

110. See Paul S. Appelbaum, *Drug-Free Research in Schizophrenia: An Overview of the Controversy*, 18 IRB: A REVIEW OF HUMAN SUBJECTS RESEARCH 1, 3 (1996).

111. See *id.* at 4.

112. See Jack Schwartz, Office of Md. Att'y Gen., Second Report of the Attorney General's Working Group app. at A-9 (May 1997) (the Second Report is reprinted in the appendix to this issue of the *Journal of Health Care Law & Policy*).

113. See Rebecca Dresser, *Mentally Disabled Research Subjects: The Enduring Policy Issues*, 276 JAMA 67, 68 (1996).

114. Federal Food, Drug and Cosmetic Act Amendments, 21 U.S.C. § 355(i) (1997).

Such regulations shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes . . . that they will inform any human beings to whom such drugs . . . are being administered . . . that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except when they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings.

See *id.*

of such arrangements, or whether a barrier must be constructed against further consent waivers.

VII. APOLOGIA

I am a philosopher, not a physician; a critic, not an investigator. Confined to taking potshots from the sidelines, I will never enjoy credit for the medical advances that will someday brighten the lives of those who are decisionally impaired.

For nearly twenty years my father took care of a young man from a middle-class family in New Jersey, a man I will call Sam. When Sam arrived at my father's hospital in 1949 he was depressed and withdrawn. After several years of institutionalization he had improved, and his family prevailed upon my father to let him go home for a long weekend. A foolish uncle, thinking that Sam must need some masculine "R&R," took Sam to a prostitute. He was unable to perform, and returned to the hospital in a profoundly depressed state that progressed to a psychosis from which he never recovered. For many years he lived in the bucolic setting of my father's sanitarium, in a room that was sparsely furnished so that he could not hurt himself. A man whose robust physique contained a gentle spirit and a painfully vulnerable person, Sam was cared for meticulously by nurses and attendants. He expressed himself mainly through high-pitched whines and bleating sounds that I will never forget. My childhood friends, upon first hearing Sam's ranting while we played on the grounds, were shocked, then curious, but quickly grew accustomed to the unworldly conversations that took place deep within Sam's soul.

Guilt-ridden, my father was determined not to repeat his earlier mistake and grew fiercely protective of his patient. An old-fashioned psychiatrist who would surely be characterized as paternalistic by later bioethicists like me, he feared the abuses to which Sam would be exposed in a state hospital. For several years, there was only one patient in the old sanitarium building in the Hudson Valley. Finally, when my father was nearly 80 years old, the insurance premiums became too expensive, and he had to give up his state license. The day of Sam's transfer was one of the saddest days that I remember in our household.

The LSD experiments on the decisionally impaired were speculative and perhaps risky, but there was nothing abstract about Sam's illness or the suffering it caused him and his family. Surely medical research with persons who are decisionally impaired must continue. How it is to be done, without undermining the very humanity it seeks to promote, will always entail an exquisitely delicate balance. That is

truly the “key note” that must be struck in efforts to guide research on this population.