Commentary

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Ethical Problems in Psychiatric Research

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Abstract

This article raises questions about the morality and value of experiments conducted mainly on psychiatric patient-subjects whose mental capacity and judgment are often impaired, making them incapable of giving informed consent. Its focus is on experimental studies in which psychotic symptoms in patients with schizophrenia have been knowingly exacerbated by suddenly withdrawing medications that they needed, administering known psychosis-producing substances such as L-dopa and apomorphine, and ignoring the treatment needs of those serving as experimental controls in placebo studies. Concerns are raised about the draft "Statement of Principles for Ethical Conduct" by the American College of Neuropsychopharmacology. Questions are also raised about the adequacy of current safeguards, including federal regulations, peer review, and the trivialization of "informed consent" by institutional review boards that operate under veils of secrecy. Implications for mental health policy are discussed, and suggestions are made for improving safeguards and reducing risks.

Unethical experiments on mental patients have been taking place in the United States for a long time. They should evoke questions about the scientists conducting them, the administrators permitting them, and the National Institute of Mental Health (NIMH) funding many of them. But because physician-researchers are regarded as holding the keys to medical advance and ultimate cures, the biomedical research community has been exempted from being held accountable lest such questions interfere with important research. Dubious experiments, violating fundamental ethical and possibly legal standards and causing human subjects pain and harm—often without their informed consent—are not, however, what the public should expect from science.

Jay Katz* recently reminded the medical bioethics community that "the oft-invoked moral right to engage in human experimentation is itself in need of a thoroughgoing examination, for that right, which finds its justification in the need to advance the frontiers of knowledge, can all too readily obliterate 'the deepest matters of our morality' by the ways in which we use human beings for our own purposes."[1]

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Evidence exists of large-scale abuse and exploitation of vulnerable, mentally disabled patients who are being used in high-risk, nontherapeutic drug withdrawal studies and in experiments using known psychosis-inducing substances which have caused uninformed patients undue pain and suffering and, in some cases, permanent damage. Therefore, current neuropsychiatric research practices with human subjects must undergo a "thoroughgoing examination" by an independent citizens group whose recommendations would be enforced.

The yardsticks for such an examination are clinical standards of treatment and the national and international codes dealing with the ethics of human experimentation, developed since the Nuremberg trial revelations of biomedical atrocities. They are the Nuremberg Code (1947),[2-6] which unequivocally established that the individual subject's rights—through informed, voluntary consent—and welfare must never be subordinated to the "interests of science and society"; the Declaration of Helsinki (1964),[7] the internationally adopted medical model that differentiated "therapeutic" and "nontherapeutic" research and required every patient, including control groups, to be ensured "the best proven diagnostic and therapeutic method"; the Belmont Report (1979),[8] the foundation for American ethical standards in research with human subjects; and the Code of Federal Regulations (Title 45, pt. 46, 1985, 1991),[9] which sets forth federal policy for the protection of human subjects and provides regulations for implementing that policy. (For a fuller discussion, see the Appendix.)

Cases Bringing Ethics in Psychiatric Research to Public Attention

The first family to question publicly the ethics of an NIMH-funded research project were the parents of 25-year-old Gregory Aller, a UCLA patient-subject who was harmed by it.

UCLA: Sudden Withdrawal of Medication From Stabilized Patients

The experiment in which Aller was involved, about which much has been written in both the lay and psychiatric media, was an 11-year, $2 million, two-part study at UCLA, "Developmental Processes in Schizophrenic Disorders," allegedly designed to gather data on the how and why of schizophrenic relapse.[10-13] The researchers specifically contrasted this study with earlier ones by defining *relapse* as "the elevation of psychiatric symptoms to the severe or extremely severe level"[14]—23 of its 50 subjects relapsed.

After his medication was suddenly withdrawn in 1990, Aller, a part-time student at UCLA, suffered more severe symptoms than in his initial episode: "My ability to concentrate fell apart. I was unable to do schoolwork. I became manic and hyperactive. Some days I would hardly sleep at all.... I started to have paranoid delusions about government agents chasing me. I became violent with my father and threatened to kill him."[15]

Another patient-subject was Elizabeth de Balogh, who now lives in a board-and-care home. "She had been stabilized for a year—able to drive and go to the beach and hold a job. But then, as she participated in the drug withdrawal protocol, her life began slipping away.... Her brother wrote government officials that when his sister began to relapse over a weekend in 1985, her family frantically tried to contact the UCLA research team by phone but only got a recorded message about the clinic's business hours."[15]

The outcome was even worse for 23-year-old Tony Lamadrid, who committed suicide in March 1991 by jumping from the roof of a ninth-story classroom. "From 1985 to 1990, he had been both a patient at the UCLA Medical Center and an active participant" in the "Developmental Processes" study. "In the spring of 1991, even though he was no longer directly involved in experiments, Lamadrid continued to be monitored by the research staff." Following his suicide, his brother wrote to the Office of Protection from Research Risks (OPRR), asking for "an inquiry into the suicide of my brother.... I have grave concerns that he may have been the victim of the questionable ethics of the professionals who were conducting research on his illness. I am personally tormented with the

responsibility of having allowed him to participate in a program that emphasized research over treatment of mental illness.... I have the horrible feeling that my brother has simply become another statistic in their research findings" (p. 18).[15]

Complaints by two families led the federal OPRR to conduct a lengthy investigation. OPRR's report concluded that "the IRB-approved informed consent documents for UCLA's Schizophrenic Disorders research failed to comply with the requirements of [federal] regulations in that they omitted certain basic elements required for legally effective informed consent: [they] failed to contain (a) adequate description of the procedures to be followed, (b) adequate description of reasonably foreseeable risks of the research; and (c) adequate disclosure of appropriate alternative procedures or courses of treatment ... as required under [federal] regulations."[17]

Cincinnati: An Unknowing Research "Control" Patient Is Given Apomorphine[18,19]

Shalmah Hawkins, a 30-year-old woman on lithium for 2 years following hospitalization for a manic-depressive episode, came to the Psychiatric Emergency Room of the Cincinnati General Hospital in January 1993, seeking help with her racing thoughts, sleeplessness, and overly elevated mood and needing a psychiatrist to adjust her medication dosage. Having no insurance, she was admitted to the research ward to take part in a "special study." Without being informed, she was assigned to serve as a "control" in a study designed to study patients with schizophrenia.

Contrary to her clinical need, but required by the research protocol, she was suddenly taken off all medication for 5 days. Her manic symptoms increased markedly: she became hostile, combative, confrontational, and, at one point, suicidal. On her fifth day, she was given a dose of apomorphine, a substance known to stimulate psychotic symptoms, and her condition worsened. Even after her lithium was resumed, her destructive behavior to herself and others continued, and she was placed in leather restraints for 3 days. Her attorney's legal brief stated that she "was not receiving treatment or therapy of any kind until lithium was reintroduced.... Rather, she was a human guinea pig, an unwitting subject of an experiment with neither the intent nor the effect of helping her."

Maryland: Procrustes Reborn—Fitting the Patient to the Research Program[20]

After 8 years of treatment, including four psychiatric hospitalizations for schizophrenia, 26-year-old Laura Becker was still disturbed, needing a high level of supervision and structure to live in the community. Hoping for better treatment success, her family brought her to the Maryland Psychiatric Research Center in the summer of 1987.* All of her medications were then stopped for a full year. "It was a terrible time," her mother wrote, "and if seeing her decompensate to a very psychotic state was distressful to me, imagine how tormenting her symptoms have been for her" (p. 17).[20]

During Laura's remaining 3½ years at the Maryland Center, she was, according to her mother, a subject in numerous research protocols, not all of them related to her condition. Though she had no history of epilepsy, she was used in a protocol testing an antiepileptic drug that was not helpful. Despite her dystonic reaction to Haldol 8 years earlier, she became part of a Haldol double-blind experiment and once again suffered a painful and frightening reaction to the drug. "For most of her 4½-year stay at the Center she was, at best, in a constantly agitated state.... At times she behaved aggressively toward both me and her father. She suffered from the severe restlessness of akathesia. Twice when I visited her, she was tied to a chair with sheets. For unexplained reasons, she lost weight to the point of being gaunt, despite added calories to her diet. There was also a period of incontinence" (p. 17).[20]

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* The Becker family has been trying for several years, with their daughter's permission, but without success and in violation of Maryland's "sunshine laws," to obtain her medical records from the Maryland Psychiatric Research Center (MPRC). Copies of their correspondence with the Director, William T. Carpenter, M.D., and the senior investigator are in the author's files.

Her mother pleaded that "the quality of life of our ill loved one . . . is an important issue that cannot be dismissed. Though research is vital to help Laura and others. . . . I doubt anyone wants to feel that they are simply a guinea pig." She then posed two questions: "was Laura's condition aggravated by the suffering she endured through those repeated washouts," and "was the ordeal she went through of significant value to research?" (p. 17).[20]

Veterans Administration, New York: "L-dopa Challenge and Relapse in Schizophrenia"[21]

Investigators at the Bronx Veterans Administration Medical Center reported their attempt "to predict time to relapse in 28 schizophrenic patients withdrawn from neuroleptics and challenged with L-dopa for seven days, then followed until relapse." L-dopa is another substance known to stimulate relapse. The patient-subjects, stabilized veterans with a history of schizophrenia and living in the community, were hospitalized for several weeks solely for this experiment. "By clinical judgment and past history [all] were in a state of remission. . . . Seven patients met the [criteria] for 'not currently mentally ill' " (p. 934).

Predictably, all 28 patients relapsed within 19 weeks. The authors claim that a "vast majority" of the patients in the study ultimately "returned to baseline levels of psychopathology" but admit that "a few did not."

The consent form signed by the patient-subjects failed to inform them that they would probably suffer relapse. Instead, it misled them by stating, "we think that by giving you this drug and evaluating your response to it, we may be able to tell if your regular medication is safe for you."[22] To explain why the consent form did not inform them of the probability that they would relapse, the researchers claimed that "at the time, the medical profession [and IRB] believed that although patients may experience symptom aggravation during neuroleptic discontinuation, it would not be advisable to talk to the patients about psychosis or relapse."[23] This claim by physicians, that producing relapse is acceptable but warning patients about its possibility is not, stands the world on its head. This particular NIMH- and VA-funded study was conducted at the Bronx VA Medical Center by psychiatric researchers from its own staff and from the Mount Sinai School of Medicine; it is currently under investigation by OPRR.

The professional literature contains many articles about "informed consent" documents whose length makes them burdensome and unintelligible. Ogloff and Otto found that informed consent forms used in psychology (and other fields) were written at an "unacceptably high reading level," leading them to question "whether participants can comprehend information contained in the consent forms." They reasoned, therefore, that "the participants who signed the informed consent forms . . . may not have been adequately informed about the studies in which they participated. Thus, their informed consent was invalid, and, strictly speaking, their participation in the research was unethical and violated federal mandates."[24] There has been no discussion in psychiatric journals known to the authors about consent documents that mislead prospective subjects of research by failing to disclose known serious risks of the experiment, such as exacerbation of symptoms and even an expectation of relapse.

Measuring These Studies Against Ethical Standards

These studies (and similar experiments) appear not to meet the ethical standards set forth in the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, the Code of Federal Regulations, and medicine's ancient ethical axiom, *primum non nocere*—first do no harm. Why, then, were they approved by IRBs, the NIMH, and the VA and then given legitimacy by publication in peer-reviewed academic journals? By what ethical or professional standards should neuropsychiatric experiments with human subjects actually be governed?

Clinical Applications of Ethics Codes

The Best-Proven Diagnostic and Therapeutic Method

The international ethical requirement to provide every patient in any medical study "the best proven diagnostic and therapeutic method"[7] means that studies failing to do so are unethical. *Best-proven methods* are, however, hard to define in psychiatry. No generally accepted clinical standards of care exist by which psychiatrists are held accountable for treatment outcomes, including research. It has been said that "psychiatry has a phobia about outcome studies. . . . Such information threatens their practice and the concepts that support it" (p. 1165).[25]

An essential aspect of that best-proven therapeutic method in every aspect of medicine is a trusting doctor-patient relationship. According to Kerr L. White, former deputy director for medical affairs of the Rockefeller Foundation, such a relationship "*seems to account for about half of the benefits* associated with medical and other health professions' ministrations."[26] That impact is even greater in psychiatry, a specialty lacking specific treatment modalities such as antibiotics and few if any accurate diagnostic tools of its own.

For centuries, the heart of effective psychiatric treatment of the mentally disabled has been competent, compassionate counseling: Philippe Pinel's work during the French Revolution,[27] the moral treatment American mental hospitals provided during the 19th century,[28] Adolf Meyer's psychobiologic approach earlier in this century linking patients' symptoms to their experiences,[29] Henri Baruk's 1978 insistence that *Patients Are People Like Us*,[30] and this senior author's 1982 report on "Effective Psychotherapy in Chronic Schizophrenia."[31]

Over the past several decades, however, biological research has replaced patient care at the top of psychiatry's value and status hierarchy, largely because of the inordinate influence of the drug industry, the ubiquitous administrative fragmentation of care,[32] and the failure of psychoanalysis (which is erroneously presented by the mass media as the only alternative to drug treatment). The treatment of schizophrenia in particular has become increasingly medication centered, whereas the therapeutic counseling that had always been the cornerstone of treatment—with or without medication—has been either ignored totally or relegated to those lacking the professional skills or credentials to assume full responsibility for the care of the individual patient. Clinical research studies have reflected this orientational shift, and the focus of most schizophrenia investigations has turned to drug trials and drug-related investigations. Unfortunately for the patients involved—and in particular violation of the Declaration of Helsinki—the research aspect of some schizophrenia drug studies has taken precedence over the well-being of the patient-subjects.

Placebo Research: Questions About Their Ethics and Science

Although refusing to engage in public discussion about the issue, the Food and Drug Administration (FDA) promotes drug washouts and placebo control studies as "the gold standard" for premarketing drug trials.* This policy and the ethics of placebo trials in general were criticized by two epidemiologists, Rothman† and Michels.[33] They reasoned that when an accepted treatment for

* The FDA has taken an untenable position by verbally and unofficially promoting drug washouts and placebo control drug trial studies when they are contrary to the interest of patients. There are no written regulations requiring such procedures; none exist for the very good reason that the requirement is not legally sanctioned: it is unethical. The FDA's published regulations follow ethical standards by allowing "the test drug [to be] compared with known effective therapy, for example, where the condition treated is such that no treatment, or administration of a placebo, would be contrary to the interest of the patient."[9] Thus it is up to researchers, administrators, and pharmaceutical executives to challenge FDA bureaucrats who require them to conduct drug trials according to protocols that violate ethical standards.

† Kenneth J. Rothman, Ph.D., is an epidemiologist at the Boston University School of Public Health and the editor of the journal *Epidemiology*.

a disorder already exists, the use of human beings as placebo controls is unethical because they are denied the benefits of existing "best therapeutic methods." They also challenged the scientific validity of placebo studies that, they maintained, provide neither evidence of efficacy—as large randomized studies do—nor scientific proof that a new treatment is better than "the best" current one. Thus, they asserted, placebo studies not only violate the ethical principles defined by Helsinki but fail to provide clinically useful information that will improve patient care.[33]

Hans Jonas, the late philosopher of religion, called deceiving patients, as in placebo control studies, intolerable: "Whatever may be said about its ethics in regard to normal subjects, especially volunteers, it is an outright betrayal of trust in regard to the patient who believes that he is receiving treatment.... The patient is definitely wronged even when not harmed. And ethics apart, the practice of such deception holds the danger of undermining the faith in the *bona fides* of treatment, the beneficial intent of the physician—the very basis of the doctor-patient relationship."[34] The widespread use of placebo control drug studies in schizophrenia—especially because the consequences for the subjects involved are known to be sometimes severe—represents an abdication of those doctors' first duty: to their patients.

Is Informed Consent Adequate?

Since the Nuremberg Code, every code of ethics has mandated that every human being has the right to be fully informed about all the potential risks and the alternative treatments available before giving (or withholding) his or her voluntary consent to serve as a research subject. Every investigator is legally and morally required to disclose fully all relevant information that would enable a potential subject to make an informed decision. The federal regulations mandate that local IRBs approve only research in which "risks to subjects are minimized, risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects.... In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research.... [It] should not consider possible long-range effects of applying knowledge gained in research."[35]

Too often signed "informed consent" forms from uncomprehending subjects have been used to justify experiments contrary to their best interests. As George J. Annas has pointed out,*[5] "a leading medical commentator, Dr. Franz J. Inglefinger, argued ... that the hospital patient is the most 'at risk' for experimentation, and that the doctrine of informed consent cannot protect patients adequately.... Incapacitated and hospitalized because of illness, frightened by strange and impersonal routines, and fearful for his health and perhaps life, [the patient] is far from exercising a free choice when the person to whom he anchors all his hopes asks, 'Say, you wouldn't mind, would you, if you joined some of the other patients ... and help us to carry out some very important research we are doing?' " Among the most vulnerable of all hospitalized patients are those with mental illness.

The late Henry K. Beecher† also pointed out how, "if suitably approached, patients will accede, on the basis of trust, to about any request their physician may make. At the same time, every experienced clinician investigator knows that patients will often submit to inconvenience and some discomfort ... but the usual patient will never agree to jeopardize seriously his health or his life for the sake of 'science.' "[36] Rothman and Michels strongly disagree that "if patients are fully informed about the risks of entering a trial and still agree to participate, there is no reason to prevent them from doing so."[33] Acknowledging that informed consent is always desirable, they maintain that "investigators should not put patients in a position in which their health and well-being could be compromised, even if the patients agree.... Despite the best efforts to inform patients, they will rarely if ever be as well informed about their treatment options as their physicians."[33]

Annas maintains that "informed consent is a necessary, but not sufficient, condition for legitimate human experimentation. A careful review of the science comes first."[5] And Robert A. Destro, professor of law and former member of the U.S. Commission on Civil Rights, states that, "as applied to persons with mental disabilities, the law of informed consent makes it clear that those consents, by patients whose very capacity to make judgments is in question, cannot be trusted. The burden of defending them rests on the persons who were charged with the duty to obtain them."[37]

Ian Chalmers, head of the Oxford U.K. Cochrane Center, part of a multinational collaboration to prepare, maintain, and disseminate systematic reviews of randomized clinical trials, calls informed consent "a fiction," pointing out that "patients in placebo-controlled trials are rarely if ever told clearly that there already exists an accepted treatment for their condition, and the risks of not getting it are not accentuated." If they were, he says, "they wouldn't go into the trials."[38] Placebo studies violate the same principles that the Tuskegee Syphilis Study did: they fail to disclose all relevant information or provide the best treatment available.

Katz states, "In 1972, I believed that the requirement of informed consent could serve as 'the primary means for implementing the abstract notion of self-determination,' and that it expressed 'society's desire to respect each individual's autonomy and his right to make choices concerning his life.' ... This has not happened.... The informed consent requirements set forth in the federal regulations on human research do not adequately address the moral issues that deserve consideration whenever human beings serve as means for the ends of others."[1] A patient's fundamental concerns as a research subject involve not only his or her rights but, even more important, his or her welfare.

Although signed informed consent forms continue to be presented by IRBs as an important aspect of their decisions to approve research protocols, Katz points out how the "low level of visibility" of local IRBs, coupled with the absence of any requirement to publish their decisions, "hampers efforts to evaluate ... [and] prevents the public at large from reacting to, what is being done for the sake of the advancement of science."[39] Annas is more blunt: "IRBs as currently constituted do not protect research subjects but rather protect the institution and the institution's investigator" (p. 331).[40] One reason is that IRBs are currently made up almost entirely of representatives of the researchers, often from the same institution. Rarely do patient-subjects have representatives on such boards.

Practice Guideline for Treatment of Patients With Schizophrenia: An APA Work in Progress[41]

An American Psychiatric Association (APA) work group has spent several years formulating a "Practice Guideline for Treatment of Patients with Schizophrenia." The immense current value and importance of its June 1994 draft needs to be quoted now, rather than waiting until the APA finally publishes it (now supposedly in the spring of 1997). According to the draft Guideline, 60% of acute schizophrenia patients will improve substantially with psychotropic drugs, but 40% will continue to exhibit psychotic symptoms (p. 25). It recognizes the need for a "supportive psychiatric management approach," stating that "whenever possible, treatment should involve an active collaboration with patients using an integrated approach with appropriate pharmacological, psychotherapeutic ... [and] rehabilitative interventions ... titrated to the patient's response" (p. 11). "The consensus is that continuity of care with a therapist who engages in a collaborative, non-authoritarian relationship will facilitate treatment and encourage the development of a therapeutic alliance. This alliance forms the foundation upon which treatment is conducted" (p. 9).

A recent meta-analysis of outcome studies over the past hundred years[42] reveals that the results for patients diagnosed with schizophrenia have worsened over the past 20, during which time the treatment focus has shifted almost entirely to drugs. Wyatt acknowledges that "in recent years, a number of studies have demonstrated that a combined program of neuroleptic administration ... and stress-reducing psychotherapy decreases the incidence of relapse in patients with schizophrenia"

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* George J. Annas, Ph.D., the chair of the Health Law Department, director of the Law, Medicine and Ethics Program, and the Edward R. Utley Professor at Boston University Schools of Medicine and Public Health, notes that the Declaration of Helsinki is "a more permissive alternative document," really an accommodation to physicians who did not like the restrictive Nuremberg Code.[6]

† Henry K. Beecher, M.D., late professor of anesthesiology at Harvard Medical School, was one of the first to examine the ethics of clinical research in his 1958 monograph *Experimentation in Man*. His 1966 landmark paper "Ethics and Clinical Research," in the *New England Journal of Medicine*, is a classic.

(p. 347).[43] Thus the APA Guideline strongly advocates a supportive integrated approach, urging psychiatrists to form "a therapeutic alliance" with patients and families to deal with problems such as "noncompliance," a serious difficulty caused largely by the severe extrapyramidal side effects (EPS)[44] occurring in 70% of patients on neuroleptic drugs. Improving side effects is "a challenge to patient-clinician collaboration"[41]—labeling patients as noncompliant is inaccurate and clinically unhelpful (pp. 38, 97).

This supports this senior author's long-held belief that such patients do recover and become productive citizens when they become active participants in their own treatment with a competent, responsible psychiatrist who helps them acquire techniques for reducing symptoms, avoiding their recurrence, and coping with life and stress—within an administrative treatment framework that fosters continuity of care.[31-33] Based on years of professional experience as a psychiatrist in state hospitals, including 5½ years as the clinical director of one of the largest, and on his own 1963 to 1964 experience as a hospitalized patient with schizophrenia, he has concluded that *schizophrenia patients should not be subjects in research without being provided with competent psychotherapy as a central component of treatment.*

Sudden "Experimental" Neuroleptic Withdrawal: Ethical and Scientific Questions

No One Questioned the Practice

A host of experimental studies has been reported over the years in which patients with schizophrenia have been subjected to sudden medication withdrawal (drug washout), often followed by placebo, despite the considerable risk of relapse these procedures produce. Such studies not only interfere with clinical treatment but often cause serious and even irreversible harm.[43]

Scrutiny of the professional literature shows that many of these studies were apparently carried out in disregard of their known impact on their patient-subjects. Ethical issues regarding patient-subjects' welfare do not appear to have been of any concern whatsoever in these studies, a conclusion based on the fact that the topic was not ever discussed in the professional psychiatric literature.

The failure of the psychiatric research community, of organized psychiatry itself, and, most important, of the National Institute of Mental Health (which funds many of these washout and induced relapse investigations) to recognize their questionable ethics, and their stony silence about the harm these studies often cause, reveals their lack of concern for the pain and suffering of psychiatrically impaired subjects—the patients they have sworn to care for. It also reveals the complete lack of both accountability and enforcement mechanisms.

Media Listen When Families Blow the Whistle

Not until relatives of affected patient-subjects brought their concerns to the mass media and the courts[45]—after being rebuffed by both the profession and the governmental agencies overseeing and funding these studies—did the profession and agencies begin to question the ethics of such research. They did not really begin paying attention until the media exposed the nature of certain peer-approved, publicly funded psychiatric experiments that harmed patients[11-15,46-48] and OPRR's report of informed consent violations had been publicized.[17]

Shamoo and Irving's article[49] first raised concerns about the lack of accountability in research using persons with mental illness. The first comprehensive published discussion of the ethics of such studies appeared in the March 1994 issue of the *Journal of the California Alliance for Mentally Ill*, "Ethics in Neurobiological Research with Human Subjects," which was coedited by this junior author.[50] In it, 30 prominent and diverse contributors examined various aspects of these issues. Shamoo assembled more than 40 published studies involving 2,482 patients in which "relapse is either part of the design or an expected consequence."[51] Of this group, "some 940 relapsed, and . . . 233 of the relapsed patients dropped out of the study." A scientist and the father of a son with mental illness, he then asked, "for whose benefit has the patient undergone pain and suffering? . . . Is anyone responsible for the harm done to someone who participates in a high risk research protocol?" A detailed presentation of his findings, submitted in 1994, finally appeared in 1996.[52]

The March 1995 issue of the *Archives of General Psychiatry* published a comprehensive review by Gilbert et al. of 66 studies of medication withdrawal between 1958 and 1993, involving 4,365 chronic schizophrenia patients.[53] They found that "the mean cumulative relapse rate was 53% in patients withdrawn from neuroleptic therapy and 16% in those maintained on it." The review was followed by a series of expert commentaries and a final response by its authors. They, and most of the commentators, agreed that the great difference in relapse rates proved that medications should not be withdrawn from patients with schizophrenia.

But, as Baldessarini and Viguera pointed out in one of the commentaries, "the sudden removal of much or all of a maintenance psychopharmacologic treatment carries an excess risk for severe symptomatic exacerbation or relapse within several months. . . . An excess of relapse following rapid drug withdrawal may inflate drug vs. no drug comparisons."[54] They also noted from Gilbert's own data that "the rate of discontinuing the neuroleptic drug may matter. Among 46 studies, 33 involved abrupt discontinuation (less than 14 days and usually 1 day) and 13 involved more gradual discontinuation (2 weeks to 2 months). The proportion of patients relapsing per month was threefold greater after abrupt discontinuation of treatment. This finding is consistent with previous observations concerning abrupt vs. gradual discontinuation of lithium in bipolar . . . disorders." This skewing of Gilbert's relapse rate by abrupt withdrawal alone—itself a poor clinical treatment strategy—means that their results are not scientifically valid measures of whether patients can go without medication.

Although such high-risk, nontherapeutic medication withdrawal experiments on patients with schizophrenia were all approved by local IRBs and by the NIMH (which funded them) and published in highly esteemed, peer-reviewed journals, it would appear that they violate national and international codes of medical research ethics. They ignored the welfare of the human beings used as subjects and failed to protect them from unnecessary harm—a fundamental requirement of every such code. And the knowledge gained from these poorly designed studies neither assists these patients' treatment nor tells us whether, or for how long, psychotropic drug treatment is really needed. Studies that exacerbate symptoms and cause patients with schizophrenia the pain of relapse are therefore both unethical and, because they are poorly designed, scientifically unsound. As Baldessarini pointed out, they fail to take into statistical account the effect of abrupt termination in increasing relapse.

Induced Schizophrenia Relapse

How can physicians conduct research on patients knowing that these experiments are likely to induce relapse and its painful consequences? Hundert, physician-ethicist at Harvard's McLean Hospital, suggests that "research is sometimes spurred by motivations baser than a desire to help humanity" and warns that society should "never, by any means, confer a 'veritable carte blanche trust' upon medical researchers."[55] For decades, the sudden withdrawal of medication from patients with schizophrenia has been recognized as in itself causing relapse, as in, for example, Denber's (1967) textbook chapter on "Tranquilizers in Psychiatry"[56] and Baldesserini's (1978) chapter on "Chemotherapy."[57] In 1991, Breggin, an outspoken critic of psychotropic drug overuse, placed a special "warning" at the beginning of his book, *Toxic Psychiatry*, that "psychiatric drugs can become dangerous when discontinued too abruptly. . . . Most have addictive qualities and can produce withdrawal symptoms that are emotionally and physically distressing and sometimes life-threatening. . . . Stopping psychiatric drugs should usually be done gradually, and only with professional guidance."[58]

Jeste et al.'s final response to the commentaries on their review points out once again that "withdrawal of treatment with antipsychotic medications, especially an abrupt one, carries a high risk of psychotic relapse in schizophrenia patients. There is little justification for repeated prolonged withdrawals of medications in chronic schizophrenia patients. . . . A very gradual and well-monitored reduction in neuroleptic dosage to the lowest effective maintenance level can be achieved in a substantial proportion of patients without precipitating relapse." They conclude (as do the APA Practice Guidelines) that "a slow taper to the lowest effective dosage may be the preferred strategy in many patients."[59]

Schizophrenia relapse has also been induced by psychosis-producing substances such as amphetamine, apomorphine, L-dopa, and PCP in patients and nonpatients.[21,60-62] Since the early 1970s, despite the high likelihood of inducing schizophrenia relapse, these drugs have been repeatedly administered experimentally to patients with schizophrenia—primarily at Veterans Administration hospitals. Yet even substance-induced relapse studies, which are clearly intended to cause patient-subjects symptom exacerbation, thus contradicting every clinical and ethical standard, have not been challenged by peer review or NIMH. Although there is no evidence that such studies have improved patient treatment, undeniable evidence such as presented here shows that they have undermined it.[21,54,63] Nevertheless, relapse-producing studies are defended by psychiatric investigators as benefiting "neuroscience."

An independent investigation by a national commission is therefore needed to evaluate the consequences of the prevailing, mostly secret, low-profile research approval process and, particularly, the absence of enforcement mechanisms. Responsibility for such research, especially invasive, high-risk studies on severely impaired psychiatric subjects, must not be allowed to remain confined to a "fraternity of silence" whose interests often conflict with, or even oppose, those of their vulnerable patient-subjects.

The Serious Potential Consequences of Psychotic Relapse

The serious, potentially long-term consequences of psychotic relapse, especially when produced by sudden medication withdrawal, were pointed out in Wyatt's comprehensive survey of the literature: "There is evidence that stable schizophrenic patients whose neuroleptics are discontinued and have relapses may have a difficult time returning to their previous level of function. . . . If a patient did relapse, the relapse was much more severe in the neuroleptic-discontinuation than in the neuroleptic-maintenance group."[43] The group off drugs "had more antisocial behavior, more self-injury and required more compulsory admissions."[43]

Wyatt also defined some of the neglected ethical aspects of harm to subjects from sudden-withdrawal studies: such "discontinuation studies raise the question of whether allowing an individual to have repeated psychotic relapses causes loss of function beyond the time of the exacerbation of the psychosis itself. . . . While it is far from clear what kind of scar prolonged or repeated psychoses might leave . . . there is ample evidence that some patients have structural brain changes as seen on pneumoencephalograms, and computer tomographic and magnetic resonance imaging scans. . . . While psychosis is undoubtedly demoralizing and stigmatizing, it may also be biologically toxic."[63]

More recently, Greden and Tandon, discussing psychotic relapse with increased paranoia, disorganization, and agitation, pointed out that it is "accompanied by major short-term negative consequences, especially impaired self-care, increased risk of aggressive behavior and harm to others, increased likelihood of hospitalization or legal confinement with attendant psychosocial and financial costs, increased risk of suicide and severe disruption of the lives of the patient and family. Since repeated withdrawals of pharmacologic treatment do contribute to more relapses . . . it is critical that clinicians seek to minimize relapse potential."[64]

The obligation to minimize relapse potential should therefore also apply to research with patient-subjects if the research is to be considered ethical. All involved patients must therefore be treated in accordance with the best-proven therapeutic method available—especially when patient-subjects are exposed repeatedly to the possibility of relapse.

Responsible Medication Reduction

A "gradual and well-monitored" medication reduction procedure, as part of a treatment methodology in which therapeutic counseling played a central role, was described in 1982 by this senior author.[31] That method is almost identical to titration reduction, regularly used medically for medications such as steroids. Dosage reduction produces increased emotionality and the emergence of some of the patient's earlier interpersonal and intrapsychic problems. But because that reduction is slow, the newly increased level of emotional intensity will also be relatively small and, therefore, manageable with therapeutic counseling. The patient's active involvement in medication reduction, as well as in his or her overall treatment, contrasts sharply with the passivity concerning both treatment and drug reduction characterizing most research studies that withhold information from the patient, thereby undermining his or her confidence in treatment.

"Science" Versus Treatment

The Inevitable Conflict Between Patient Care and Detached, "Objective" Research

Research "divorced from clinical practice . . . runs the risk of being uninformed by the real phenomena that the clinician, family member and recipient struggle with daily. The *reductio ad absurdum* . . . is a research endeavor that follows its own internal logic (i.e. to generate publications and receive research grants) but which is, in fact, insensitive to the real issues" of the patients.[65] Inducing "experimental" relapse in stabilized patients with schizophrenia is cruel and inhumane: the significantly high rate of relapse in the studies cited here suggests that patient treatment was subordinated to the goal of collecting research data, thus rendering these studies unethical. As Irving* cautions, "Individuals with mental illness suffer enough as it is. They should not be further burdened—and personally harmed—by taking part in basic experimental research which is for the greater good of society, or for the greater good of future psychiatric patients, or for the advancement of scientific knowledge."*,[66]

Katz refers to an "endemic moral tension" between two conflicting moral values: the advancement of knowledge for the benefit of society and the requirement of protecting the inviolability of human research subjects: "The recent revelations about the radiation experiments conducted by governmental agencies and the medical profession once again confront us with the human and societal costs of too relentless a pursuit of knowledge at the expense of moral values. If this is a price worth paying, society should be forced to make these difficult moral choices in bright sunlight and through the regulatory process that constantly strives to articulate, confront and delimit the costs" (p. 14).[67]

The American College of Neuropsychopharmacology's Position[68]

The American College of Neuropsychopharmacology (ACNP) takes a very different view. Disregarding ethical codes since Nuremberg and defying federal law, its recent draft "Statement of Principles of Ethical Conduct for Neuropsychopharmacologic Research in Human Subjects" places its members' interests ahead of the welfare of the disabled patients it uses as subjects by maintaining that, "although minimizing risk relative to benefit is a goal of research, the uncertainty regarding the outcome of the research makes the precise estimation of the risk difficult at the outset of a research study. . . . Notwithstanding the substantial benefit to society derived from neuropsychopharma-

* Dianne N. Irving, Ph.D., formerly a research biochemist at the National Institutes of Health and the National Cancer Institute, is now an associate professor of the history of philosophy and ethics at the DeSales School of Theology in Washington, DC.

cologic research, another societal interest that must be considered is the welfare of each research subject. This must be viewed in the context of the risk that will occur in the absence of scientific progress. . . . It should be emphasized that advances in medical research with subsequent benefit to society are impossible without individual risk" (pp. 1-4).[68]

The attitude conveyed in the ACNP "Statement of Principles" about the steps needed to ensure the safety of their subjects whose mental faculties are severely impaired seems quite cavalier and disturbing. Many of these patients' ability to comprehend and to make reasoned choices is often compromised and can thus be easily exploited. ACNP's insistence that "in experimentation it is impossible to predetermine the exact scope of the risks. . . . The existence of this uncertainty and . . . the limits of knowledge concerning the experiment should not itself be a cause for abandoning the research" contradicts the Declaration of Helsinki's principles that "physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that *the hazards involved are believed to be predictable*" and should "be prepared to terminate the experiment if 'continuation is likely to result in injury . . . to the experimental subject' " (I, 7; emphasis added). What then is adequate "cause" to the ACNP for "abandoning the research?"

Even more striking in these ACNP "Principles" is a profound contradiction of the fundamental American principle that everyone has the equal right "to life, liberty and the pursuit of happiness." The ACNP claims instead that "*all persons living in society have a moral responsibility to participate in efforts to promote and contribute to the present and future welfare of that society. Research is one of those obligations*" (p. 3, emphasis added).

Such an outrageous claim would radically alter the accepted moral values of our society: it could never be defended by ACNP within the larger academic community. If brought before the general public, such a radical claim would be rejected; no one has an obligation of any kind to participate in any kind of research.

Such an ideology of an elite corps of neuropsychiatric researchers who conduct experiments "with investigational agents that affect the brain, and/or the peripheral nervous system, and behavior" on mentally impaired persons, and who are currently in an unchallenged position to implement that ideology, raises profound moral questions. Before ACNP members apply these "Principles" to human subjects, certain fundamental questions must first be publicly examined in light of the "Principles" and their implications: is society prepared to consign special groups for "selection," whose members are then to assume "individual risks" for the sake of "scientific progress . . . advances of medical research . . . or the future welfare of society?" Who has the moral or legal authority to determine who will "select" these human research subjects? Can society entrust its mentally impaired, powerless citizens to researchers whose "Principles of Ethical Conduct" disregard and contradict established national and international leg nd ethical norms?

This "Statement of Principles," from an organization whose membership (by invitation only) eschews open discussion, reveals a most disquieting premise: that the value of its members' research transcends the value of individual persons—particularly those who are severely impaired mentally, lack competence, and consequently cannot exercise rational autonomy. ACNP makes the self-serving but unsupportable assertion that its members' "significant contributions to human welfare" entitle them to be authorized evaluators of the risk/benefit ratios acceptable in experiments on others. But these researchers' evaluation of risks is made both in the proclaimed context of potential "future scientific benefits" and in the unacknowledged context of their own personal current benefits. That conflict of interest should disqualify them from making decisions about the real "individual risks" patients are expected to assume for the "subsequent benefit for society." What "risks and sacrifices" are ACNP members prepared to make personally to attain that "present and future welfare of society"?

Furthermore, contrary to legal informed consent requirements, ACNP researchers claim that they may "deceive the subject concerning the nature of the experimental intervention" (pp. 2, 12). This would even further legitimatize the devaluation of persons who are mentally impaired to nonhuman status. Irving warns that "if this 'logic' is pushed, then the mentally ill (including those with schizophrenia), Alzheimer's and Parkinson's patients, drug addicts, alcoholics, etc. could easily be rendered 'non-persons' too (which did in fact happen in Nazi Germany)."[66] The Nazis first reduced people with mental illness to the status of nonpersons and had them "voluntarily" sterilized while developing on such institutionalized patients the technology of gassing, which they first applied to such patients and then to millions of others.[69-73]

Response of the Profession and Public Oversight Agencies

Attempts to Suppress Discussion

Free and open exchange of ideas is the hallmark of scientific freedom in a democratic society. The psychiatric research community has, for the most part, shunned open debate about its practices and impact on patient-subjects. When questioned about the ethics of relapse experiments, NIMH has denied any problems. ACNP has attempted to suppress public discussion: a week before the January 1995 "First Annual Conference on Ethics in Neurobiological Research with Human Subjects" in Baltimore,[74-76] ACNP president David Kupfer advised ACNP participants that "it is inappropriate for ACNP to support or participate in the Baltimore Ethics Conference . . . chaired by Dr. Shamoo."* Publication of the latter's paper criticizing the ethics of medication washout studies was then suddenly withheld.†[52]

Following the publication of the March 1995 issue of the *Archives of General Psychiatry*,[33,54,59,64] the senior author of this article and others submitted letters criticizing the NIMH for funding, and thereby condoning, unethical psychiatric research. The editor's response ignored the ethical issues and instead reaffirmed the need for more studies; no letters of criticism were published.

The OPRR's Findings and Self-Contradictory Conclusions

OPRR's report criticized UCLA's IRB for approving the protocols that "omitted certain basic elements required for legally effective informed consent," faulted its protocols for failing to provide adequate safeguards, and found the practice of "whiting out" records unacceptable.‡[,17] Despite these and other violations, the agency, in what appears to be a contradiction of its own findings, concluded that the research was "scientifically and ethically justifiable."

UCLA continues to deny OPRR's findings and its own responsibility: responding to the report, "UCLA declined to implement OPRR's recommendation to contact former subjects, citing concern that 'they might experience needless alarm' and . . . were already aware of their *individualized* relapse/exacerbation experiences on and/or off medication."[17] Thus UCLA (like Mount Sinai/Bronx VA[23]) asserts that exposing patients to relapse is acceptable, but warning them of the possibility of relapse is not. This specious position represents an attempt to avoid compliance with ethical and legal requirements for full disclosure, hiding from patient-subjects the nature and inherent risks of the experiments. Only after OPRR's final report on the UCLA study was released and questions

* Memorandum from D.J. Kupfer, M.D., the president of ACNP, to members of the Baltimore conference organizing committee, December 29, 1994, in the author's file.

† A June 9, 1994, letter from Margaret Dorrier, the managing editor of the *Journal of Clinical Ethics*, informed Dr. Adil Shamoo that his article "Intentionally Causing Relapse: Breakdown in Ethics" had been accepted for publication. Galley proofs for publication in the winter 1994 issue accompanied an October 21, 1994, letter to him from Melissa Maxfield, managing editor. Early in November 1994, a telephone call from the editor-in-chief, Edmund G. Howe, M.D., J.D., advised Dr. Shamoo that the article had been widely circulated in manuscript form and that because of pressure from an unnamed investigator and threats against the publisher, it would not be published in the winter issue (letters and galley pages are in the author's files). The article appeared under a different title in the *Cambridge Quarterly of Health Care Ethics*.[53]

‡ The OPRR report describes two protocols as the basis for these studies.[17] The first, "Developmental Processes in Schizophrenic Disorders," required a fixed dose of depot-Prolixine. The second, "Double-Blind Drug Cross-Over and Withdrawal of Neuroleptics in Remitted, Recent-Onset Schizophrenia," involved medication withdrawal.

were raised in the media did NIMH even begin to consider the subject; a year later, it offered a research grant for a project on "Informed Consent in Clinical Mental Health Research."

An Unsanctioned Proposition

Neuropsychiatric researchers justify their noncompliance with ethical standards requiring full disclosure of risks by claiming that there are "moral imperatives of medical research with human subjects"[77] and implying that these imperatives supersede accepted ethical standards. What "moral imperatives" have Americans sanctioned or agreed on? Certainly not the supremacy of research "for the good of future generations" ranking above an individual's right to dignity and autonomy. Despite OPRR's critical report, the psychiatric research community has continued to deny any ethical problems while shielding their colleagues (and their own questionable studies) with their silence. Indeed, some of its leaders rallied to UCLA's defense and even attempted to intimidate those complaining about such experiments.* Because there has been no acknowledgment of the need to reform the safeguards for vulnerable patient-subjects of psychiatric research, the issues have not been resolved, and a cloud hangs over much of psychiatric research.

The Presumed Altruism of Patients With Mental Illness

Frederick Goodwin, M.D., a former director of NIMH, dismisses concerns for the welfare of psychiatric patients in research by claiming that serving as research subjects may indeed be their most important contribution to society: "We must not allow appropriate protections to obscure the fact that, more often than not, participation in research is a remarkably positive experience for patients. For many, research participation affords the first opportunity in their experience of illness to see the possibility that some good may be derived from their illness. For many subjects, the knowledge that their participation will help others who have the same or other mental disorders is a cause for increased—and justified—self-esteem."[78]

At the 1995 Baltimore Ethics Conference, Goodwin, Kane, and Carpenter claimed that "an exquisite degree of cooperation exists between investigator, subject and often their families" and argued that full disclosure and enforcement of true informed consent would interfere unnecessarily with the "opportunity . . . to help others."[†] But Katz questions that claim's authenticity, stating that "such cooperation . . . cannot be presumed," and, "if it exists at all, it must be grounded in a prior explicit mutual understanding of the competing interests that bring the parties together" (p. 5).[67]

Disclosure of Risks Conflicts With Researchers' Interests

Researchers fear that full disclosure of the risks involved would dissuade prospective subjects from consenting to participate. Thus fear of losing a readily available pool of uninformed, and therefore willing, subjects underlies the researchers' efforts to evade such required disclosure. A fundamental yet unacknowledged conflict of interests consequently permeates the entire research enterprise. Medical researchers have a tremendous stake in the highly profitable and competitive medical research establishment that, they fear, would be compromised by enforcing the Helsinki

* Dr. Carpenter, the director of the MPRC, publicly attempted at the January 1995 Baltimore ethics conference to intimidate Mrs. Janice Becker, whose critical account of her daughter's 4½ years as a patient-subject there is described earlier.[20] In a January 5, 1996, letter to Dan E. Weisburd, the editor and publisher of the *Journal of the California Alliance for the Mentally Ill*, Dr. Carpenter questioned his integrity and made false allegations concerning two editorial decisions relating to the "Ethics in Neurobiological Research" issue.[49] Weisburd's response of February 14, 1996, affirms the authenticity of her account, cites articles written by Carpenter about the experiments she described, and clarifies why UCLA's "side" of its schizophrenia relapse project was not published: its attorneys forbade it (letters are in the author's files).

† John M. Kane, M.D., a professor of psychiatry at Albert Einstein College of Medicine and the chairman of the department of psychiatry at Hillside Hospital-Long Island Jewish Medical Center.

standards. Given the reality of this existing conflict of interests, Katz sees it as all the more important for the potential subject to be better protected and more fully informed than is customary about the risks of subordinating his or her own therapeutic interests and becoming a subject in an experimental research protocol that offers no direct benefit.

The Profession Continues to Ignore the Consequences of Relapse "Experiments"

In August 1995, the *Archives of General Psychiatry* published a paper by Van Kammen et al., "Behavioral vs. Biochemical Prediction of Clinical Stability Following Haloperidol Withdrawal in Schizophrenia."[79] The paper was accepted on March 29—after publication of the "Neuroleptic Withdrawal in Schizophrenia" papers in March 1995.* This "experiment" involved 88 male veterans with chronic schizophrenia who had been stabilized in the community but were admitted to the hospital for 8 to 10 weeks solely for the study. Their medications were immediately discontinued and replaced by Haldol for 2 to 4 weeks; they were then subjected to painful lumbar puncture and retained in the hospital without medication for at least 6 more weeks to see who would relapse. The paper does not state how many did.

The investigators hoped that examination of spinal fluid and of observed behavioral changes immediately after medication withdrawal would enable them to predict the likelihood of relapse. But such attempts to reduce experimental investigations of psychiatric patients to painful technological tinkering seriously ignore both the inherent dignity of each patient and the proper role of the physician in the doctor-patient relationship. The investigators' admission that "many patients in the prodromal phase do not share emerging psychotic symptoms with therapists" demonstrates the consequence of these physicians' detached mode of dealing with their patient-subjects. Fifty of these human beings had been subjects in these investigators' earlier government-funded studies. In this study, they were again denied the "best diagnostic and therapeutic method" (II, 3)[7] and again put at substantial risk of relapse, without being offered any personal benefit. The researchers indicate that they plan to conduct similar relapse prediction studies.

The *Archives*' editorial comment on this paper, written as though the questions raised in its March issue never existed, says its authors "produced a better prediction rate" from their research, implying that similar reports on "identifying patients at increased relapse risk due to medication non-compliance" would be welcomed (p. 619).[80] The ethics of continuing to expose patients to relapse from sudden medication withdrawal is thus ignored by the profession. If and whether the agonies suffered by those individuals who were put through unnecessary experimental relapse improved their care or other patients' care or even provided any general scientific knowledge remain unclear. The only obvious beneficiaries are the researchers and the drug companies on whose behalf many of these studies were conducted.

Drug Researchers Exaggerate the Frequency of Relapse Without Medication

Pharmaceutical companies have greatly influenced the nature of psychiatric research and treatment; yet contrary to the inflated claims of neuropsychopharmacologists, whose financial interests are closely entwined with the industry's, these efforts have yet to show evidence of significant improved treatment outcomes for patients.

Although most clinical psychiatric research involves drugs, an accepted part of the treatment of schizophrenia and other disorders, drugs do not represent the entire treatment needs of individuals suffering from that illness. The efficacy of drugs and the alleged total failure of all other treatment before and without them have been greatly overstated over the years, especially when a new drug

* In contrast, Nancy Andreasen, M.D., Ph.D., the editor of the *American Journal of Psychiatry*, announced in the fall of 1994 that *AJP* would no longer accept research reports without detailed information about proper informed consent procedures.[93]

is marketed. These inflated expectations have produced misguided mental health policies, resulting in overall therapeutic neglect and poor treatment outcomes. A meta-analysis of the literature over the past 100 years reveals a weighted average improvement of 40% in patients with schizophrenia followed up for 10 or more years—about 48% improved in the 1960s and 1970s. However, despite our highly publicized, alleged treatment advances, only 38% have improved in the 1990s.[42]

The implications of current high relapse rates, reported as 60% to 90% among first-episode patients with schizophrenia after medication withdrawal, must therefore be examined more closely.[63] A 5-year follow-up of all first admissions to the New York State Hospital system in 1943 (not mentioned in the meta-analysis and before the advent of psychotropic drugs) revealed that 44% of patients with schizophrenia were not readmitted after discharge (56% of the cohort relapsed or remained hospitalized).[81] Similarly, in 1950, Hillside Hospital's 4-year follow-up of patients diagnosed with schizophrenia found that 52% did not need readmission; 48% had relapsed and needed rehospitalization.[82,83] The data contradicts claims such as Angrist's that "a diagnosis of schizophrenia in the pre-neuroleptic era was equivalent to being told that one would probably spend the remainder of one's life in a state hospital."[84] Such claims also ignore the fact that today patients with schizophrenia seem to relapse and require rehospitalization much more frequently than their predecessors did.

Too many clinicians and researchers have shifted their primary, sometimes their entire, focus to the short-term effects of new drugs, even to the point of paying little attention to how those drugs are administered after hospital discharge, and their long-term effects on patients—thus obscuring the worsening care patients are receiving. In many cases, they now get no aftercare at all.[32] Much of Wyatt's 60% to 90% relapse rate represents induced relapses from abrupt medication withdrawal by "noncompliant" patients who distrust their doctors. Praising the efficacy of medications on the basis of poor clinical practices that lead to relapse is therefore not scientifically valid. And abrupt medication withdrawal, under all but emergency circumstances, is highly unethical.

Implications for Mental Health Policy and Administration

Nontherapeutic drug washouts and placebo control studies, in which the conditions of patients with schizophrenia have been aggravated, have become alarmingly widespread in psychiatric research. This failure of some neuropsychiatric research to comply with biomedical ethical standards, by placing the acquisition of scientific data ahead of the welfare of patient-subjects, should lead mental health policy makers and administrators to reevaluate how they exercise their authority to ensure that the welfare of patients at their institutions is not undermined. After all, the primary reason for the existence of mental health facilities is to provide care to their patients: research at such facilities should be important only insofar as it either benefits them directly or indirectly while causing them no harm.

When treatment is the primary focus of a psychiatrist's relationship with his or her patient-subjects, he or she works with them, and research findings are regarded as products of experimental treatment; the clinician's primary concern then remains, as it should be, the patient's welfare. When, however, patient care is subordinated to the needs of research, the experiment becomes the team's primary focus, patients become mere subjects of studies, and doctors experiment *on* them. When treatment needs thus take a backseat, patient-subjects are at risk of not receiving the best-proven diagnostic and therapeutic method. Such "treatment" can, in fact, be in many ways antithetical, if not antagonistic, to the individual patient-subject's well-being. Professional treatment standards for patients with schizophrenia were defined in the APA "Practice Guideline." It is the responsibility of administrators to ensure that those standards are met for *all* patients—particularly those participating in research, either as subjects or as controls.

IRBs and the Trivialization of "Informed Consent"

America's current low-profile institutional process for approving, overseeing, and evaluating research places responsibility entirely on IRBs for such experiments on vulnerable patients with mental impairments. IRBs, composed mostly of medical researchers, represent the interests of and are primarily concerned with scientific research rather than patient-subjects' welfare. It is therefore not surprising that these boards, whose members are those with the greatest interest in conducting research, have approved protocols that place vulnerable subjects with mental impairments at high risk of harm. IRBs have routinely approved pharmaceutical company-funded experimental studies requiring nontherapeutic drug washouts and placebo control trials that have exacerbated painful psychotic symptoms and schizophrenia relapse. In so doing, they have failed to safeguard these patients' welfare.

Since Nuremberg, the right not to be used in medical research unless one personally gives "voluntary, competent, informed, and comprehending consent" has been every human being's explicit right. But signed consent forms, which IRBs routinely accept, do not prove a study's legitimacy, its ethical standards, or its scientific value. Nor are they sufficient evidence that patients have given truly informed consent as required by law. This is particularly obvious when "informed consent" from noncomprehending, cognitively impaired patients has been submitted and accepted. IRB members usually ask few probing questions for fear of "embarrassing" colleagues who may sit on grant-awarding committees.

The composition of IRBs must consequently be restructured to include independent patient representatives and members of the community to ensure adequate safeguards for patients' welfare and genuine ethical compliance. Chief administrators must exercise their authority and establish accountable review mechanisms that will examine research proposals to ensure that each study has at least the potential of benefiting the patients involved without posing serious risk of harm. Administrators must ensure that the research tail does not wag the therapeutic dog; they must not allow patient care at their institutions to be compromised by serving solely or primarily the interests of investigators who, too often, have unacknowledged financial conflicts of interest.

As a civilized society, policy makers have a moral responsibility to ensure that our vulnerable citizens—including psychiatric patients—are not conscripted as guinea pigs into high-risk, nontherapeutic experimental research solely "for the sake of scientific progress." In particular, decisions affecting patient-subjects' rights and welfare cannot remain the exclusive domain of a self-appointed "fraternity of silence," the American College of Neuropsychopharmacology, whose "Statement of Principles of Ethical Conduct" itself raises grave ethical concerns. These "principles" serve only to legitimatize ACNP's dubious utilitarian ethic that gives this elite group permission to impose on people with mental illness a publicly unsanctioned "moral responsibility."* How long will it take before mental health policy makers and administrators intervene on behalf of this vulnerable patient population, whose disabled condition renders them defenseless as human beings but highly desirable as research subjects?

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* After submitting this paper for publication, the authors obtained a copy of a later version of ACNP's "Statement of Principles" as "approved by Council and the membership in Feb., 1996." It is currently under further revision. This version, prepared after neuropsychiatric research with human subjects had come under intense public criticism, is liberally sprinkled with statements designed to show concern with subjects' welfare (e.g., "researchers have a responsibility to society to protect the welfare of each subject . . . risk can and should be minimized by safeguards in study design") but remains silent about implementation mechanisms, resisting any independent evaluation or oversight that would indeed protect those subjects. Thus ACNP continues to claim its right to apply a different standard of informed consent and full disclosure of risks to its psychiatrically impaired human subjects whom, it maintains, "it is possible to deceive." Furthermore, ACNP's repetition of the earlier caution against using the "Statement of Principles" "retrospectively to judge research conducted prior to its adoption by the ACNP" suggests that such research had indeed been conducted without a framework of ethical standards, and a major reason for issuing the new "Principles" was the protection of the researchers being criticized.

Families, ethicists, and lawyers are questioning the ethics, scientific legitimacy, and high risks of these improper experiments and demanding accountability for harmful outcomes from the institutions involved. The facts cannot be eradicated with "white-out" or remain hidden; the ethical implications of dubious neuropsychiatric experiments—which were published and should have raised questions long ago in the psychiatric community and public oversight agencies—are still not being examined.

The Courts Intervene[85-89]

The failure of policy makers and psychiatric researchers to set guidelines limiting research on mentally impaired persons has led the courts to place limits on experiments involving persons with psychiatric impairments, including children, who cannot give informed consent. In a landmark case (*TD v. NYS OMH*), New York State Supreme Court Justice Edward Greenfield opened his decision by stating, "The mere mention of experimental medical research on incapacitated human beings—the mentally ill, the profoundly retarded and minor children—summons up visceral reactions with recollections of the brutal Nazi experimentation with helpless subjects in concentration camps, and elicits shudders of revulsion when parallels are suggested. Even without the planned brutality, we have had deplorable instances of overreaching medical research in this country."[85]

Greenfield ruled on February 28, 1995, that the State Office of Mental Health (NYS OMH) lacked authority to authorize "surrogate" approvals for nontherapeutic research involving institutionalized human beings incapable of giving informed consent and struck down as "invalid and unenforceable" OMH's regulations permitting such approvals. On March 20, 1995, the court ordered a halt to all such "non-therapeutic, greater-than-minimal-risk experiments on incapable patients based on surrogate consent" and ordered NYS OMH to "withdraw all patients who are subjects of research without lawful authority . . . [and] to notify in writing each patient withdrawn from research, or the legally authorized guardian . . . that the patient was a subject of research without legal authorization." OMH was enjoined "from conducting all non-federally funded research until . . . OMH complies with the state's Public Health Law [and] . . . from conducting research on patients deemed incapable of consenting to the research."[86,87]

New York's appeal for an automatic stay, which is almost always granted, was denied.[88] New York Lawyers for the Public Interest, the plaintiffs' attorneys, explained that the "appeals court took the rare step of lifting the stay—a strong showing of the court's concern for the irreparable harm faced by the patients, as well as an endorsement of the likelihood that the plaintiffs would win the appeal."[89] When NYS OMH continued these experiments, plaintiffs moved to hold the state in contempt. On January 18, 1996, the court ordered the state to "cease . . . all non-therapeutic . . . experiments on incapable patients" in state-licensed facilities.

Without specific reference to the Declaration of Helsinki, the Court followed its standards by defining *therapeutic research* as "research [that] . . . holds out a prospect of direct benefit that is important to the health or well-being of the patient, is available only in the context of research . . . [and is] in the subject's best interest."[88] Overall, the decision could have affected 400 psychiatric experiments that had been approved and about $52 million worth of research overseen by OMH. Under pressure by the press and the plaintiffs' attorneys, OMH admitted that about 100 individuals, 85 of them children, have been affected by the January order.[90] Similar cases are now before other courts: in Houston, Texas, a state district judge has issued a temporary restraining order barring any research on involuntarily committed psychiatric patients at Harris County Psychiatric Center, which is operated by the University of Texas.[91]

As medical ethicist, David Thomasma cautions, "For those who are vulnerable in a modern scientific society, greater care must be taken for their vulnerability. . . . The only research that can ethically be conducted on the neurobiologically impaired is that which either benefits them directly, or benefits the class of such beings directly, themselves only indirectly, but poses either no or only very mild risk."[*,92]

Suggested Guidelines for Mental Health Administrators

Mental health administrators must ensure that research with mentally impaired persons is moral and ethical, professional responsibilities are clearly defined, and adequate safeguards are adopted and implemented. These include the following:

1. Explicit recognition of the codified national and international ethical standards—the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, the Code of Federal Regulations—requiring that
   - the fundamental right to "voluntary, competent, informed and comprehending consent" may not be waived (Nuremberg);
   - "adequate preparation [be taken] to protect the experimental subject against even the remote possibilities of injury, disability or death" (Nuremberg);
   - "the interests of science and society should never take precedence over considerations related to the well-being of the subject" (Helsinki, III, 4);
   - "the potential benefits, hazards and discomfort [of the proposed study] should be weighed against the advantages of the best current diagnostic and therapeutic methods, [with] every patient—including those of a control group if any—being assured of the best proven diagnostic and therapeutic method" (Helsinki, II, 2).
2. Federal law requires local institutions to formulate and implement expanded regulations to protect persons with mental impairments who are especially vulnerable to abuse and exploitation because of their dependency on and availability at public institutions and clinics. That federal requirement must be implemented to provide the added safeguards needed by this population, similar to those mandated for other vulnerable populations (i.e., prisoners, children, pregnant women).
3. Implementation guidelines and procedures must be established to reduce risk of harm and to ensure enforcement of ethical and legal requirements.
4. Patient representatives on IRBs must be included whenever they consider research involving subjects with mental illness in above-minimal risk experiments.
5. Federal requirements for full disclosure of risks, including the possibility of relapse and major drug-related risks disclosed in the *Physicians' Desk Reference*, must be enforced.
6. Independent clinicians not associated with the institution must evaluate patient-subjects' competency to provide "informed consent," observe the obtaining of these consents, and monitor these subjects for the duration of the study to ensure their continued consent.
7. The process of obtaining informed consent and disclosure of risks should be videotaped.
8. Mechanisms for follow-up monitoring and care for at least 1 year after the research, both for patients completing the study and those who drop out, must be provided.
9. Disclosure of funding sources for the study on consent forms must be required.

A Legacy of Shame

The psychiatric community's blind eye and deaf ear to ethical violations by some of its members should make administrators even more aware of the urgency for improving enforcement mechanisms to protect human subjects of psychiatric research from exploitation.

Dr. Ewen Cameron was one of the world's most honored psychiatrists; president of the American, Canadian, and World Psychiatric Associations, he became notorious for his 1950s "deprogramming [and other] dangerous, bizarre, intrusive experiments, [which were] often performed with no regard for the welfare of the human subject."[93,94] Rubenstein,† an attorney who represented Cameron's patient-victims, points out that "*the remarkable aspect of the research is that it was all published in*

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* David C. Thomasma, Ph.D.; Fr. Michael L. English, S.J., a professor of medical ethics in and the director of the Medical Humanities Program, Loyola University Chicago Medical Center.

† Leonard S. Rubenstein, the executive director of the Bazelon Center for Mental Health Law, was one of the lawyers for the victims of Cameron's experiments in litigation against the CIA.

major journals and . . . presented before sophisticated professional audiences. And yet, no one said a word about informed consent, possible harm to patients, potential conflicts between Cameron's research agenda and the needs of the people who came to him for ordinary help."[95] Further evidence of psychiatry's lack of self-discipline and penchant for "convincing" patients to undergo radical "treatments" are the more than 50,000 lobotomies performed in this country.[96] Has nothing been learned since?

If, in today's climate of suspicion and frustration, publicly funded institutions fail to address these issues forthrightly, they will lose public support, and their administrators will be held accountable for whatever experimental research is conducted at their facilities.[97,98] When the public learns that public funds have supported unethical experimentation, causing unnecessary pain and suffering to disabled citizens while withholding effective treatment from them, it is unlikely to be tolerant. The mere mention of Dr. Henry Foster's minimal involvement in the Tuskegee Syphilis Study disqualified him from consideration for a Cabinet position. Mental health administrators may be called on to defend publicly before courts of law the research activities at their institutions and, like the now-discredited tobacco company magnates, may even be called before congressional investigative hearings to explain their personal roles in human rights violations in their own facilities.[99]

References

1. Katz J: "Ethics and clinical research" revisited: A tribute to Henry K. Beecher. *Hastings Center Report* 1993; 25(5):31-39.
2. Annas GJ, Grodin MA (Eds.): *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation*. New York: Oxford University Press, 1992.
3. Grodin MA: Historical origins of the Nuremberg Code. In: Annas GJ, Grodin MA (Eds.): *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation*. New York: Oxford University Press, 1992, pp. 121-144.
4. Caplan AL: Are existing safeguards adequate? *Journal of the California Alliance for the Mentally Ill* 1994; 5(1):36-38.
5. Annas GJ: Experimentation and research. *Journal of the California Alliance for the Mentally Ill* 1994; 5(1):9-11.
6. Annas GJ: The changing landscape of human experimentation: Nuremberg, Helsinki, and beyond. *Health Matrix—Journal of Law and Medicine* 1992; 2:119-140.
7. Declaration of Helsinki IV, World Medical Association, 18th World Medical Assembly, 1964; amended Hong Kong, September, 1989. Council for International Organizations of Medical Sciences (CIOMS), Geneva, 1993.
8. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: *Report and Recommendations: Research Involving Those Institutionalized as Mentally Infirm* [The Belmont Report]. DHEW Pub. No. (05) 78-0006. Washington, DC: U.S. Department of Health, Education and Welfare, 1979.
9. 45 Code of Federal Regulations (CFR) 46, 1985; revised 1991.
10. Agency says UCLA erred in medical experiments. *Reuters*, March 9, 1994.
11. Hilts PJ: Agency faults a UCLA study for suffering of mental patients. *New York Times*, March 10, 1994, p. A-1.
12. Garrett L: Closer tabs on human research urged. *Newsday*, March 11, 1994, p. A-17.
13. When the patient is also an experiment [Editorial]. *Los Angeles Times*, March 11, 1994, p. B-6.
14. Medical ethics in the dock [Editorial]. *New York Times*, March 14, 1994, p. A-16.
15. Horowitz J: For the sake of science. *Los Angeles Times Magazine*, September 11, 1994, pp. 16ff.
16. Subotnik KL, Neuchterlein KN: Prodromal signs and symptoms in schizophrenia relapse. *Journal of Abnormal Psychology* 1988; 97(4):405-412.
17. Office for Protection from Research Risks, Division of Human Subject Protections: *Evaluation of Human Subject Protections in Schizophrenia Research Conducted by the University of California, Los Angeles*. Washington, DC: U.S. Department of Health and Human Services, May 11, 1994.
18. Hawkins-Prince SL: Personal communication, December, 1994.
19. Thompson DI: Memorandum in opposition (on behalf of) Shalmah Lee Prince v. David L. Garver, M.D., et al., U.S. District Court, So. Dist. of Ohio, Western Division, October, 1995.
20. Becker JC: A mother's testimony. *Journal of the California Alliance for the Mentally Ill* 1994; 5(1):17.
21. Davidson M, Keefe RSE, Mohs RC, et al.: L-dopa challenge and relapse in schizophrenia. *American Journal of Psychiatry* 1987; 144:934-938.
22. Department of Veterans Affairs, Bronx Medical Center: Consent forms for two-part-study: Neuroleptic withdrawal and Sinemet (L-dopa); obtained by author under FOIA [no date].
23. Davidson M: personal communication, May 16, 1994.
24. Ogloff JRP, Otto RK: Are research participants truly informed? Readability of informed consent forms used in research. *Ethics & Behavior* 1991; 1(4):239-252.
25. Dorwart RA, Adler D, Berlant J, et al.: Taking issue: Outcomes assessment and psychiatric services. *Hospital and Community Psychiatry* 1994; 45(December):1165.
26. White KL: *Healing the Schism: Epidemiology, Medicine and the Public's Health*. New York: Springer-Verlag, 1991.
27. Pinel P: *A Treatise on Insanity*. Davis DD (Trans.). New York: Hafner, 1962.
28. Bockoven JS: *Moral Treatment in American Psychiatry*. New York: Springer, 1963.
29. Meyer A: *Psychobiology: A Study of Man*. Springfield, IL: Charles C Thomas, 1957.
30. Baruk H: *Patients Are People Like Us: The Experiences of Half a Century in Neuropsychiatry*. Finlatter E, Ayer J (Trans.). New York: Morrow, 1978.
31. Lehrman NS: Effective psychotherapy in chronic schizophrenia. *American Journal of Psychoanalysis* 1982; 42:121-132.
32. Lehrman NS: The bureaucratic destruction of patients' faith in their doctors: Public psychiatry's negative lessons for general medicine. *Bulletin of the New York Academy of Medicine* 1994; 71:194-217.
33. Rothman KJ, Michels KB: The continuing unethical use of placebo controls. *New England Journal of Medicine* 1994; 331:394-398.
34. Jonas H: Philosophical reflections on experimenting with human subjects. In: Freund PA (Ed.): *Experimentation with Human Subjects*. New York: Braziler, 1969, pp. 1-31.
35. 21 Code of Federal Regulations (CFR) ch. 1 (April 1, 1993 ed.): 314.126 (b) (2) (iv).
36. Beecher HK: Ethics and clinical research. *New England Journal of Medicine* 1966; 274:1354-1360.
37. Destro RA: Law, professionalism, and bad attitude. *Journal of the California Alliance for the Mentally Ill* 1994; 5(1):50-53.
38. Taubes G: Use of placebo controls in clinical trials disputed. *Science* 1991; 267:25-26.
39. Katz J: Human experimentation and human rights. *Health Law Symposium: St. Louis University Law Journal* 1993; 38(1):7-54.
40. Annas GJ: *Judging medicine*. Clifton, NJ: Humana, 1988, p. 331.
41. Herz MI, Hawkins LL, Liberman RP, et al.: *Practice Guidelines for Treatment of Patients with Schizophrenia, Work Group on Schizophrenia*. Draft 1A. Washington, DC: American Psychiatric Association, June 1994.
42. Hegarty JD, Baldessarini RJ, Tohen M, et al.: One hundred years of schizophrenia: A meta-analysis of the outcome literature. *American Journal of Psychiatry* 1994; 151:1409-1416.
43. Wyatt RJ: Neuroleptics and the natural course of schizophrenia. *Schizophrenia Bulletin* 1991; 17(2):325-351.
44. Van Putten T: Why do schizophrenic patients refuse to take drugs? *Archives of General Psychiatry* 1974; 32:67-72.
45. Willwerth J: Tinkering with madness. *Time*, August 30, 1993, pp. 40-41.
46. Schizophrenic's case spurs review of consent guidelines. *Los Angeles Times*, July 13, 1994, p. A-5.
47. Lehmann C: Family testimony reveals human dimension of UCLA schizophrenia research controversy. *Psychiatric News*, March 17, 1995, pp. 13-14.
48. Families tell their side of suicides. *Santa Monica Outlook*, August 13, 1995.
49. Shamoo AE, Irving DN: Accountability in research using persons with mental illness. *Accountability in Research* 1993; 3:1-17.
50. Sharav VH, Weisburd DE (Eds.): Ethics in neurobiological research with human subjects [Special issue]. *Journal of the California Alliance for the Mentally Ill* 1994; 5(1):1-69.
51. Shamoo AE: Our responsibility toward persons with mental illness as human subjects in research. *Journal of the California Alliance for the Mentally Ill* 1994; 5(1):14-16.
52. Shamoo AE, Keay TJ: Ethical concerns about relapse studies. *Cambridge Quarterly of Health Care Ethics* 1996; 5:373-386.
53. Gilbert PL, Harris MJ, McAdams LA, et al.: Neuroleptic withdrawal in schizophrenic patients. *Archives of General Psychiatry* 1995; 52:173-186.
54. Baldessarini RJ, Viguera AC: Neuroleptic withdrawal in schizophrenic patients. *Archives of General Psychiatry* 1995; 52:189-191.
55. Ghaemi SN, Hundert EM: The ethics of research in mental illness. *Journal of the California Alliance for the Mentally Ill* 1994; 5(1):47-49.
56. Denber HCB: Tranquilizers in psychiatry. In: Freedman AM, Kaplan HI, Kaplan HS (Eds.): *Comprehensive textbook of psychiatry*. Baltimore, MD: Williams & Wilkins, 1967, pp. 1251-1262.
57. Baldessarini RJ: Chemotherapy. In: Nicholi AM (Ed.): *Harvard Guide to Modern Psychiatry*. Cambridge, MA: Harvard University Press, 1978, pp. 387-432.
58. Breggin PR: *Toxic Psychiatry: Why Therapy, Empathy, and Love Must Replace the Drugs, Electroshock, and Biochemical Theories of the "New Psychiatry."* New York: St. Martin's, 1991.
59. Jeste DV, Gilbert PL, McAdams LA, et al.: Considering neuroleptic maintenance and taper on a continuum. *Archives of General Psychiatry* 1995; 52:209-212.
60. Wolkin A, Angrist B, Wolf A, et al.: Effects of amphetamines on local cerebral metabolism in normal and schizophrenic subjects as determined by positive emission tomography. *Psychopharmacology* 1987; 92(2):241-246.
61. Daniel DG, Weinberger, DG, Jones DW, et al.: The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia. *Journal of Neuroscience* 1991; 11:1907-1917.

62. Szymanski S, Lieberman J, Pollack S, et al.: Clozapine effects on neuroendocrine responses to apomorphine challenge in chronic schizophrenia. *Biological Psychiatry* 1995; 37(1):52-55.
63. Wyatt RJ: Risks of withdrawing antipsychotic medications. *Archives of General Psychiatry* 1995; 52:205-208.
64. Greden JF, Tandon R: Long term treatment for lifetime disorders? *Archives of General Psychiatry* 1995; 52:197-200.
65. Opler LA: Conducting clinical psychiatric research in "non-research" settings. *Journal of the California Alliance for the Mentally Ill* 1994; 5(1):30-31.
66. Irving DN: Psychiatric research: Reality check. *Journal of the California Alliance for the Mentally Ill* 1994; 5(1):42-44.
67. Katz J: Final reflections. In: Shamoo A (Ed.): *Ethics in Neurobiological Research with Human Subjects*. Buffalo, NY: Gordon Breach Science, 1996, pp. 331-337.
68. Klein DF, Schooler N: A statement of principles of ethical conduct for neuropsychopharmacologic research in human subjects. Draft revision, November 1995, American College of Neuropsychopharmacology.
69. Caplan A (Ed.): *When Medicine Went Mad*. Totoa, NJ: Humana, 1992.
70. Wertham F: *A Sign for Cain*. London: Robert Hale, 1966.
71. Mitscherlich F, Mielke F: *The Death Doctors*. London: Elek, 1962.
72. Muller-Hill B: *Murderous Science*. Oxford, UK: Oxford University Press, 1988.
73. Proctor RN: *Racial Hygiene: Medicine under the Nazis*. Cambridge, MA: Harvard University Press, 1988.
74. Hilts PJ: Consensus on ethics in research is elusive. *New York Times*, January 15, 1995, p. 24.
75. Burd, S: Researchers, advocates for mental patients clash over U.S. rules. *Chronicle of Higher Education*, January 20, 1995, p. A29.
76. Horvitz LA: Ethics study focuses on mentally ill. *Insight*, March 27, 1995, pp. 14-17.
77. Lieberman JA: The moral imperatives of medical research in human subjects. *Journal of the California Alliance for the Mentally Ill* 1994; 5(1):40-41.
78. Goodwin FK: Questions and answers. *Journal of the California Alliance for the Mentally Ill* 1994; 5(1):45-47.
79. Van Kammen DP, Kelley ME, Gurklis JA, et al.: Behavioral vs. biochemical prediction of clinical stability following haloperidol withdrawal in schizophrenia. *Archives of General Psychiatry* 1995; 52:673-678.
80. This month in AGP. *Archives of General Psychiatry* 1995; 52:619.
81. Lehrman NS: A state hospital population five years after admission: A yardstick for evaluative comparison of follow-up studies. *Psychiatric Quarterly* 1960; 34:658-681.
82. Rachlin HL, Goldman GS, Gurvitz M, et al.: Follow-up study of 317 patients discharged from Hillside Hospital in 1950. *Journal of the Hillside Hospital* 1956; 5:17-25.
83. Lehrman NS: Follow-up of brief and prolonged psychiatric hospitalization. *Comprehensive Psychiatry* 1961; 2:227-240.
84. Angrist B: Ethical issues regarding prospective studies of amphetamine psychosis. *Journal of the California Alliance for the Mentally Ill* 1994; 5(1):32-33.
85. T.D. v. NYS OMH, 626 N.Y.S.2d 1015 (Sup. Ct. NYCnty 1995); Court order: Docket Order 5136/91 (Sup. Ct. NY Cnty) 3/20/95.
86. Hilts PJ: Judge tells health department to stop experiments on patients. *New York Times*, March 26, 1995, p. A-13.
87. Two courts put limits on research involving the mentally ill. *Chronicle of Higher Education*, March 31, 1995, p. A-27.
88. T.D. v. NYS OMH: Appellate Div. Order: Docket No. M-3213, 8/3/95; Appellate Div. [no docket no.] order denying motion to vacate, 1/29/96.
89. Lowenkron R, Zucker C: Court orders state to cease dangerous experiments on psychiatric patients. Press release, January 22, 1996, New York Lawyers for the Public Interest.
90. Mooney M: Halts drug testing on mental patients. *Daily News*, January 24, 1996, p. 12.
91. Psychiatric hospital told to halt tests. *Fort Worth Star-Telegram*, February 18, 1995.
92. Thomasma, DC: Obtaining consent for research in the neurobiologically impaired. *Journal of the California Alliance for the Mentally Ill* 1994; 5(1):54-55.
93. Willwerth J: Madness in fine print. *Time*, November 7, 1994, p. 63.
94. Weinstein, HM: *Psychiatry and the CIA: Victims of mind control*. Washington, DC: APA, 1990.
95. Rubenstein LS: Psychiatric experimentation: The lessons of history. *Journal of the California Alliance for the Mentally Ill* 1994; 5(1):22-24.
96. Hilchey T: Dr. James Watts, 90, pioneer in use of frontal lobotomy [Obituary]. *New York Times*, November 11, 1994, p. B-7.
97. Wong D: Neuropsychiatric hospital on probation. *Daily Bruin*, April 18, 1995, p. 1.
98. Shuit DP: Three top officials will leave UCLA clinic. *Los Angeles Times*, April 19, 1995, pp. B-1, B-4.
99. Hilts PJ: House panel told of more tests done without consent. *New York Times*, May 24, 1994, p. A-13.
100. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: *Summing up*. Washington DC: Government Printing Office, 1983.
101. Appelbaum P, Lidz C, Meisel A: *Informed consent—legal theory and clinical practice*. Oxford, UK: Oxford University Press, 1987.

APPENDIX

Codifications of the Ethics of Human Experimentation

The Nuremberg Code (1947)[2]

The Nuremberg Code, considered "the cornerstone of modern human experimentation ethics,"[3] was part of the court decision that convicted Nazi physicians of crimes against humanity. As Arthur Caplan, the Director of the Center for Bioethics of the University of Pennsylvania Medical Center, points out, "the Code did not as much articulate a new level of ethical protection for those involved in medical research as it did reaffirm an old one," going back to Hippocrates and medicine's ancient ethical axiom, *primum non nocere*—first do no harm.[4]

The Code, which became the international standard and prototype of all later codes, differentiated sharply between the rights and the welfare of experimental subjects. To protect subjects' rights, the first and foremost requirement of the Code is that subjects give "voluntary, competent, informed and comprehending consent."[5] To protect the subjects' welfare, the Code mandates the principles for such experiments: that they be scientifically valid with results "unprocurable by other methods," that "anticipated results" and "humanitarian importance" justify the risks, and that "adequate preparation" is taken to "protect the experimental subject against even the remote possibilities of injury, disability or death," with the researcher being "prepared to terminate the experiment if 'continuation is likely to result' " in any of those consequences.[6]

The Declaration of Helsinki (1964)[7]

The 1964 Declaration of Helsinki, adopted by the international community, including the United States, amplified the Nuremberg Code in important ways. In its introduction, the Declaration defines *therapeutic* and *nontherapeutic* research and requires that "in the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific without implying direct therapeutic value to the person subjected to the research."[8] This medical ethics model establishes the following standards for all biomedical research involving human subjects:

(a) Its "potential benefits, hazards and discomfort should be weighed against the advantages of the best current diagnostic and therapeutic methods. . . . In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method" (II, 2).
(b) "The interests of science and society should never take precedence over considerations related to the well-being of the subject" (III, 4).
(c) It "should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society" (I, 5).
(d) "Physicians should abstain from . . . projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable" (I, 7).

Unfortunately, the Nuremberg Code and the declarations . . . did not have much of an impact in the United States," as Caplan pointed out,[4] even though Americans assumed that they did. In his 1966 landmark *New England Journal of Medicine* article, "Ethics and Clinical Research," Henry K. Beecher, the eminent Harvard medical researcher and ethicist, described 50 American medical experiments that violated ethical standards: "an experiment is ethical or not at its inception" and "ends do not justify means."[36]

The Belmont Report (1979)[8]

Revelations in 1973 about the Tuskegee Syphilis Study[4] outraged the American public. Its outcry led Congress to create in 1974 the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, whose recommendations, embodied in the Belmont Report, laid the foundation for American ethical standards in research with human subjects.[8] Its recommendations led to (1) the adoption of a federal policy for the protection of human subjects, (2) the adoption of federal regulations to protect human subjects in federally supported research, (3) the establishment of the federal OPRR to ensure compliance with the policy, and (4) the establishment of local IRBs.

The Belmont Report identified especially vulnerable groups for whom it recommended special federal protections—disadvantaged Blacks, mentally disabled patients—especially the institutionalized—prisoners, and children.[8] The Report recognized that "owing to their ready availability in settings where research is conducted," these groups may, for "administrative convenience," be sought as subjects for research (p. 8). It therefore stated that, "given their dependent status and their frequently compromised capacity for free consent, they should be protected."

The Code of Federal Regulations (CFR, 1985, revised 1991)[9]

Title 45 of the Code of Federal Regulations, Part 46, sets forth federal policy for the protection of human subjects and provides regulations for implementing that policy. Although the CFR recognizes persons with mental disabilities as a vulnerable group, as well as children, prisoners, pregnant women,[100] and economically or educationally deprived persons—all of whom need additional safeguards—none of these safeguards has been adopted for their protection, even though the other vulnerable groups have received them.[49] That additional layer of protection, to compensate for their special vulnerability to exploitation—which their dependence and administrative availability make relatively easy—has been withheld as "the result in large part of opposition from researchers on mental disorders, who claimed that the populations in question were no more vulnerable than most persons with severe medical disorders and that the suggested limitations would seriously restrict research on mental disorders."[101]

The federal government thus has left policies and procedures governing experimental studies involving people with mental illness, and their welfare as well, largely to local IRBs.[9] But members of local IRBs are mostly medical researchers, often from the same institution, representing the interests of and being primarily concerned with scientific research rather than patient-subjects' welfare. In essence, people with mental illness have been left to be protected by those with the greatest interest in using them as research subjects; this government-approved protocol thus has assigned the fox to guard the chickens.