

them. The methodologic problems of studying the brain and behavior and the clinical burdens of working with psychiatric patients have contributed to this problem in the past but are abating at present. It would be unfortunate if the NBAC's attempts to address the problem of impaired capacity not only were incomplete and ineffective but also had the unintended effect of impeding research on mental illness.

If the mentally ill are different in a way that raises questions about their civil liberties and prevents them from participating in research, and if psychiatric research is dangerous and researchers are not to be trusted, the strategy recommended by the NBAC has merit. On the other hand, if persons with psychiatric disorders are as able and entitled as those without such disorders to take part in and benefit from research, if creative researchers can design valuable, yet safe studies, if clinicians and researchers regularly place their research subjects' interests first, and if the public, patients, ethicists, researchers, and clinicians all share a common goal, then it is time to expand the dialogue and collect data about the strengths and weaknesses of the current system. We should search for solutions that will protect all persons who have impaired decision-making capacity without further stigmatizing the mentally ill, undermining the research agenda for mental illness, or diluting the moral responsibility of researchers.

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ETHICAL AND HUMAN-RIGHTS ISSUES IN RESEARCH ON MENTAL DISORDERS THAT MAY AFFECT DECISION-MAKING CAPACITY

FOR research with human subjects, the more things change, the more they remain the same. In the 50-odd years since the 10 principles of the Nuremberg Code were set forth by the U.S. judges who convicted the Nazi concentration-camp physicians of crimes against humanity, the tensions inherent in using human beings as a means to advance biomedical knowledge have surfaced repeatedly. Ever more detailed codes and regulations from governments as well as professional bodies, such as the World Medical Association in its oft-revised Declaration of Helsinki,¹ have not put the subject to rest. Indeed, the lesson of the past half-century is that suffering, death, and violation of human rights can arise not only when dictators give inhumane scientists free rein to treat human beings as guinea pigs,^{2,3} but also when well-meaning physicians conduct research in a free and enlightened society.⁴⁻⁶

The most recent evidence of this phenomenon can be seen in two sets of problems: those associated with local supervision of research with human subjects in general and those that arise in psychiatric research, particularly that involving children and patients who are unable to make informed, voluntary decisions about their participation in such research. The two types of problems have come together in a number of instances, as investigators and institutions conducting research on mental disorders have been found by courts and federal bureaus, such as the Office for Protection from Research Risks at the National Institutes of Health, to have violated applicable statutes and regulations.

In a series of reports released in June 1998, the inspector general of the Department of Health and Human Services concluded that reforms were need-

ed in the system of review by institutional review boards (IRBs) at both the local and the national level.⁷ Since the passage of the 1974 National Research Act, universities and other research centers have been required to use IRBs to protect the rights and welfare of human subjects. Research institutions provide the Department of Health and Human Services with single- or multiproject assurances that their IRBs will apply the federal rules to all federally funded research conducted at the institution or by its employees; many assurances encompass all research with human subjects regardless of sponsorship. The inspector general concluded that the IRB system is in jeopardy because the local boards are overworked, they fail to oversee approved studies, their members lack sufficient training, and they face inherent conflicts of interest.⁷ These problems persist because the Office for Protection from Research Risks and its counterparts in other departments have neither the resources nor the independence to provide adequate guidance to IRBs, much less to monitor their activities.

Nowhere have the problems with this delegation of federal authority been more apparent in recent times than in research on mental disorders. There have been press accounts of abuses at major institutions — particularly a series in the *Boston Globe* in November 1998⁸ that concluded with an editorial calling on the Justice Department to conduct a criminal investigation — as well as congressional hearings on studies in which mental symptoms were provoked through either the withdrawal of medication or the administration of drug challenges to psychiatric patients or children.

The difficulties run deeper than inept review by IRBs or inadequate consent forms.⁹ They involve not only the actions of individual researchers or the failings of their institutions but also conflicts over principles and objectives in the entire enterprise of medical research. These conflicts have not been — and may never be — resolved. Developing knowledge about human diseases and their treatment ultimately depends on using people as experimental animals. As articulated in the Nuremberg Code and reaffirmed since then, exposing people to risk in the name of science becomes licit only with their informed, voluntary consent. Today we add to that requirement the prior review of research protocols by IRBs to weed out projects whose scientific merit does not justify their risks and to ensure that accurate and understandable descriptions of the research will be conveyed to subjects. Yet even if IRBs did their job perfectly, their approval was never intended to substitute for consent freely provided by potential research subjects.

What, then, should happen when research focuses on conditions that interfere with a person's capacity to provide informed consent? Not too long ago, the prevailing view was that when consent could not be obtained (because of the mental incapacity of a child

or a person with a mental disorder) "procedures which are of no direct benefit and which might carry risk of harm to the subject should not be undertaken."¹⁰ Over the past 30 years, however, two exceptions have seriously eroded the prohibition against enrolling incapacitated subjects in research protocols. First, it now seems widely accepted that research would be unnecessarily impeded if such subjects could not be enrolled with the permission of their guardians when the research presents no more than minimal risk. Second, guardians may also enroll patients who lack decision-making capacity in riskier research that can reasonably be predicted to provide the patient with direct benefits that would otherwise be unattainable. Many of the problematic situations regarding research with mentally impaired subjects are connected to the second exception. It is the first, however, that actually raises graver issues.

THE PROBLEMS OF THERAPEUTIC RESEARCH

The Nuremberg Code — framed, as it was, in the context of research in concentration camps on unconsenting prisoners — made no exception for therapeutic intent in its consent requirements. The World Medical Association, however, reflected the prevailing medical view when it framed the 1964 Declaration of Helsinki around the "fundamental distinction . . . between clinical research in which the aim is essentially therapeutic for a patient, and clinical research the essential object of which is purely scientific and without therapeutic intent."¹¹ Although this articulation of the categories is seriously flawed,¹¹ the conclusion that "therapeutic research" should be subject to more relaxed standards of consent was incorporated into U.S. policies by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research — for example, in its 1977 report on research involving children,¹² which led to federal regulations, and its 1978 report on institutionalized mentally infirm patients,¹³ which never became part of the regulations regarding research on human subjects.

Yet the conventional formulation has it backwards. As a general rule, as I have written elsewhere, we should "set higher requirements for consent" and "impose additional safeguards on therapy combined with experimentation [than on research with normal volunteers], lest investigators even unwittingly expose 'consenting' patient-subjects to unreasonable risks."¹⁴ The risk is not simply that patients who are recruited for research will become victims of what is called the therapeutic misconception — that is, construing research interventions as advantageous (especially when no other proven intervention exists) even when the prospect of benefit is in truth nonexistent or at best extremely remote.

The greater risk is that everyone involved, from the investigator to the members of the IRB to soci-

ety at large, will allow this misconception to blind them to the reality that the entire rationale for supporting and pursuing research is that even the careful accumulation of observations derived from treatment interventions (in which choices are framed in terms of what is best for a particular patient) is not an adequate way to produce reliable, generalizable medical knowledge. Rather, the achievement of such knowledge requires a scientific approach in which, as Hans Jonas cogently observed, the subject of research is not an agent any longer but a "mere token or 'sample' . . . acted upon for an extraneous end without being engaged in a real relation."¹⁵ Indeed, a collective therapeutic misconception may lie behind the shift in the paradigm over the past decade: today, many investigators, IRB members, and commentators alike apparently think the primary ethical requirement is no longer to protect research subjects from harm (especially in the case of those least able to protect themselves) but to avoid the perceived injustice of excluding potential subjects from studies.

There may be no medical field in which the limited effectiveness of available treatments generates more persistent despair among patients, their families, and physicians than mental illness. This despair is particularly evident with respect to conditions that radically compromise their victims' ability to function successfully in the world, to be themselves, and to enjoy the sense of safety and stability that most people take for granted. That sense of desperation has led to a willingness to permit research in which the potential for harm would lead any rational person to decline to participate. IRBs have, for example, approved "wash-out" studies, in which medications that successfully prevent symptoms in patients with schizophrenia are withdrawn, apparently on the basis of the investigators' suggestion that such studies offer the prospect of benefit because antipsychotic medication can have harmful side effects and some patients successfully stop medication after a while. But if the real purpose of the study is to develop criteria for predicting which patients are most likely to relapse, and if the manner and timing of the washout are dictated by the protocol rather than by the needs or preferences of individual patients, it is wrong to characterize the study as aiming to provide subjects with benefit, which will occur adventitiously if at all.⁹

ASSESSING THE CAPACITY TO CONSENT TO PARTICIPATE IN RESEARCH

The dangers in lowering standards of protection in therapeutic research are exacerbated for patients whose disorder may impair their capacity to make decisions. For this reason, the National Bioethics Advisory Commission, of which I am a member, recently recommended that IRBs "should require that an independent, qualified professional assess the potential subject's capacity to consent" to any protocol presenting more than minimal risk, unless the inves-

tigator provides good reasons for using less formal assessment procedures (recommendation 8).¹⁶ This recommendation was criticized on the grounds that such assessments would stigmatize patients with mental disorders insofar as they are not routine for research on the medically ill. However, it would not stigmatize potential subjects in the world's eyes to tell them that the research design requires that their capacity to consent be evaluated, since that information would remain entirely within the confidential relationship between the potential subjects and those carrying out the research project. As any competent patient should quickly realize, such a requirement reflects no disrespect for potential subjects, though it may indicate some concern about the conflicting motives of researchers.

Nor are the norms of fairness violated by imposing such a requirement when none exists for research in other areas. Even if empirical investigation showed that decision-making capacity is just as likely to be as compromised among patients suffering from other medical conditions as among those with mental illness, it is not prejudicial to insist that investigators take reasonable steps to make sure that subjects whose condition directly affects the brain can actually provide voluntary, informed consent. The objection based on unequal treatment would seem much more fitting if researchers on mental disorders already routinely used appropriate means to assess their subjects' decision-making capacity and were simply urging that investigators in other areas be held to the same standard. The National Bioethics Advisory Commission reviewed protocols for a number of recently published studies of mental disorders, all of which involved more than minimal risk to participants. Many involved patients with serious psychiatric conditions. Not a single protocol gave evidence of any effort on the part of the researchers to assess subjects' decision-making capacity. Nor was such a requirement apparently imposed by any IRB in approving these protocols.

The failures, if any, of researchers in other fields do not excuse the lack of attention on the part of psychiatric researchers to one of the basic prerequisites for ethical research. Insisting that the capacity to consent be appropriately assessed does not contradict the presumption, which applies to patients with mental disorders as to every other potential research subject, that all adults are competent. Ignoring the *prima facie* need for some evaluation of the ability to consent makes a mockery of that presumption by rendering it nothing more than a convenient rationale for ignoring the fact that the consent obtained from some subjects may not be valid.

The National Bioethics Advisory Commission further concluded that, whether or not the research offers the prospect of direct medical benefit to subjects, the enrollment of a subject depends on one of three procedures: informed consent, if the subject

has decision-making capacity; "prospective authorization" for a particular class of research, given when the subject was still competent; or permission from a legally authorized representative chosen by the subject or from a concerned relative or friend who is available to monitor the subject's involvement in the research and who will base decisions about participation on "a best estimation of what the subject would have chosen if [still] capable of making a decision" (recommendations 11 through 14).¹⁶ Moreover, even when research is intended to benefit subjects, objection by any subject (even one who lacks decision-making capacity) to enrolling or continuing in a protocol "must be heeded" (recommendation 7).¹⁶

THE USE OF PATIENTS IN RESEARCH TO BENEFIT OTHER PATIENTS

As compared with the harm that has arisen from the more lenient standards for therapeutic research, the other exception to the requirement of personal consent — namely, allowing guardians to enroll incapacitated subjects when the research presents no more than minimal risk of harm to the patient — may seem not to be problematic. Any difficulties this exception creates would seem to center around the vagueness of the term "minimal risk." Yet this exception has far-reaching, troubling effects.

The exception arose initially in the context of research with children. A flat prohibition against using children in research that provides them no direct benefit was seen as a barrier not only to conducting medical examinations and similar procedures to accumulate data on normal functioning, but also to using standard psychological tests or observational tools. Some theorists argued that guardians' permission should be honored as vicarious consent in such situations (on the presumption that, were they capable of deciding, children as reasonable people would recognize their obligation to aid the community) and as an exercise of appropriate paternalism (that is, a guardian by volunteering a child's participation is teaching the child the importance of sacrifice for the sake of others).¹⁷ Even more important was the idea that parents' choice to expose their children to the risks of everyday life encompasses children's enrollment in research studies posing minimal risk. The same reasoning was then applied to other potential subjects who lacked the capacity to make decisions for themselves, including adults with various illnesses and injuries.

The exception for studies posing no more than minimal risk establishes the principle that it is acceptable to expose unconsenting people to some risk — not for their own direct good, but for the good of some larger group. But if minimal risk is acceptable, what about permitting participation when there is a minor increase over minimal risk? That is precisely what the National Commission for the Protection of Human Subjects recommended in 1977¹² and the

Department of Health and Human Services adopted for research with children in 1983.¹⁸ Furthermore, the regulations link the allowable interventions to those inherent in subjects' "actual or expected medical, dental, psychological, social, or educational situation," meaning that greater risks and burdens may be imposed on sick children than on healthy ones.

Psychiatric researchers urged the National Bioethics Advisory Commission to adopt a similar approach for people whose mental disorders prevented them from consenting to participate in research. This is what an advisory group in New York did when it recommended allowing surrogate decision makers to permit persons incapacitated with respect to decision making to participate in nonbeneficial research that presented a minor increase in risk over the minimal level.¹⁹ The commission, however, rejected the creation of this intermediate category, whose nebulous nature only compounds the vagueness of minimal risk.

"Minor increase" is just the camel's head and neck following the nose of "minimal risk" into the tent. The flexible nature of these categories invites a relativist view, in which the addition of a little burden or risk to the lives of patients with chronic mental illnesses can easily be justified by the prospect of substantially advancing medical knowledge. Once IRBs become used to this way of thinking, it is easily applied not just to federally funded basic research but also to clinical trials of new drugs, which are less likely to advance scientific knowledge than to offer financial rewards to the pharmaceutical manufacturers that sponsor the trials and the clinicians who are paid to conduct them.

THE NEED TO CONFRONT PROBLEMS OPENLY AND SOLVE THEM

Occasionally, research may offer the prospect of developing critical knowledge about a disease or ways of treating it that cannot be obtained in any other way than by studying subjects who have the disease. If all who suffer from the condition are permanently unable to decide for themselves whether to participate in the research, and if it would be impossible for them to agree in advance to become subjects and to appoint a representative to make decisions on their behalf, then society may wish to ask whether this might be the rare case in which researchers may add the risk of injury to the insult of the illness that already burdens the patients.

An affirmative response to that question amounts to placing some especially vulnerable people in a role that, however worthy, is not one that they have chosen. If such a step is to receive the thoughtful attention it deserves, it should be confronted openly, not behind the doors of a local IRB but in a much more public forum. And the group that considers it must do what IRBs seldom do — namely, look at every aspect of the study design (has everything possible been done to reduce the chance of injury and

to ameliorate any adverse event that does occur?), the selection of subjects (among all who suffer from the disease, why was this group chosen, and are no others available who are more able to assent or object to their participation?), the reliance on surrogate decision making (are the people asked to provide permission for these subjects actually able to do so in an informed, voluntary fashion?), and the claimed infeasibility of obtaining the subjects' consent (is the condition one in which prospective authorization is truly impossible, or is it merely inconvenient for the researchers?).

It seems likely that a body will be established to consider just such issues. Steven Hyman, the director of the National Institute of Mental Health (NIMH), has announced plans to create a new review panel to screen high-risk intramural and extramural studies funded by the institute. He also plans to eliminate "some of the repetitious 'me-too' studies in the intramural portfolio," in a separate initiative that is linked to the creation of the new review body "by a desire to make sure that the science in NIMH studies is good enough to justify the use of human subjects."²⁰

Dr. Hyman may hope his move will blunt the effect of the recommendation by the National Bioethics Advisory Commission that the secretary of the Department of Health and Human Services appoint a special standing panel to review protocols that IRBs would be unable to approve on their own under the commission's proposed regulations (recommendation 2). The reason to assign this task to a national panel is to provide a process that is more visible, more knowledgeable, and more independent than can be expected from many IRBs. The special standing panel would review principally protocols that expose subjects to greater than minimal risk yet are not intended to benefit them directly and for which the subjects are not able to give informed consent and have not previously provided prospective authorization (recommendation 12). Besides approving studies employing methods that an IRB regards as posing more than minimal risk to participants, the special standing panel could in time reclassify some of these methods as ones that IRBs could approve for particular types of research with specified groups, without further review and approval by the panel. The guiding principle, as the commission puts it, is that the special standing panel should never "approve a protocol that reasonable, competent persons would decline to enter."¹⁶ That principle does not resolve the tension inherent in research involving incapacitated persons, but at least it does not hide it.

Experience over the past two decades has made clear the need for special protection for patients with

mental disorders. The regulations and official actions — as well as the recommendations for IRBs — of the National Bioethics Advisory Commission are the minimum needed. The federal government should adopt them without further delay.

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