as soon as may be warranted. One should note that patients, in everyday life, do decide to stop treatment for many reasons. These experimental designs do mirror everyday life and help to explain the effects of patient's decisions to terminate treatment.

Q-How are conflicts of interest avoided?

A-First, any investigator who is a standing member of a local IRB is not allowed to participate in the review of his or her own research application. Institutions are required to establish safeguards to prevent employees, consultants, or members of governing bodies from using their positions for purposes that are or give the appearance of being motivated by a desire for private financial gain for themselves or others such as family or business associates.

Q-Who protects vulnerable patient-subjects from being exploited?

A-Protection from exploitation is the shared responsibility of the principal investigator, all other members of the research and treatment team, the legal guardian or patient's family (at the discretion of the patient), the local IRB, and, ultimately the government, extending from the Public Health Service's OPRR to local laws and courts.

Conclusion

While our system of specific checks and controls against exploitation of research participants is increasingly extensive and detailed, 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.

I am pleased to have had the opportunity to participate in this important discussion. Readers with additional questions are invited to write to NIMH, and we will refer them to additional sources of information. ■

THE ETHICS OF RESEARCH IN MENTAL ILLNESS

by S. Nassir Ghaemi, M.D. and Edward M. Hundert, M.D.

The most ancient and widely accepted ethical axiom of medicine is *"Primum Non Nocere:" First Do No Harm.* This ethical principle, enunciated by Hippocrates in his **Epidemics** over 2300 years ago, comprises the minimal moral code of medicine. Whether or not you help the patient, the principle says, at least make sure you do not hurt the patient.

In medical research, as in medical practice, this principle may seem limiting sometimes. Chemotherapy that may cure a cancer can also lead to a fatal complication. A research drug may be found not to help the patient who is its subject; if that fact were known before the study, there would be no need to conduct the research; but learning that fact would prevent others from unnecessarily receiving that drug. As with chemotherapy, there is the chance that research may actually harm the patient who is subject to it.

So what should be done? In both medical practice and medical research, doing *"no harm"* has never meant that treatment plans or experimental protocols must be completely risk free. When research ethics became the subject of intense interest after the Nazi atrocities of WWII, ***Primum Non Nocere*** was interpreted to mean that researchers have to reduce known risks to the lowest possible level and that any remaining possible risks must be fully disclosed to people being recruited as subjects, so that they can make an informed choice about whether to volunteer for the study. In recent years, attention has been placed not only on risks to the subject's physical and psychological health, but to the preservation of the person's rights and autonomy as well.

Research in mental illness is even more complicated than research in medicine in general. In the 17th century, Descartes and other philosophers divided the human being into mind and body, and asserted that the mind was wholly spiritual and the body wholly physical. They denied any connection between the two phenomena. Whatever one may think about this philosophical dualism today, it has seeped into the consciousness of Western culture over the last three centuries. In particular, it "freed up the body" for scientific research. Before Descartes, the Church and popular prejudice stifled research on the human body; anatomists had to steal corpses from graveyards, and physiologists could only work with animals. After Descartes, society began to accept experimentation on the human body, rationalizing spiritual concerns away by locating them in the protected incorporeal mind, which was left alone. The issue of research in mental illness was left untouched for hundreds of years.

For the patient with mental illness, his or her main demands are ***personal respect and the best available treatment.*** To those ends, ethicist Bernard Lo writes that the main ethical principles currently accepted in medical research are the following:

1. The principle of beneficence asserts that the research be potentially beneficial to the patient. These benefits should outweigh any risks presented by the research.

2. The principle of justice asserts that the research should benefit other patients, if it is not directly beneficial to the patient.

3. The principle of autonomy asserts that the patient's rights as a human

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being, as a *"person"* in contrast to as a *"patient,"* need to be respected; he or she must be assured of confidentiality; he or she must have the option to give or withhold informed consent; he or she should by no means be coerced in any way.

While the medical research community may verbally accept these principles, do they put them into practice? The short answer seems to be: *"Usually."* The mechanisms for implementation of these principles are relatively minimal. In 1974, the U.S . Government established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and since then has created the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, the Ethics Advisory Board, and the Biomedical Ethics Advisory Committee. All of these boards and committees exist on an ad hoc basis, however, meaning that they only function intermittently. A recent report from the Congressional Office of Technology Assessment entitled, **"Biomedical Ethics in U.S. Public Policy,"** reviewed the function of these entities and concluded that they were largely successful; however, it recommended that a permanent federal entity be established to guide federal policy continuously on the ethics of medical research.

The principle of autonomy asserts that the patient's rights as a human being, as a *'person'* in contrast to as a *'patient,'* need to be respected; he or she must be assured of confidentiality; he or she must have the option to give or withhold informed consent; he or she should by no means be coerced in any way.

The National Institutes of Health, which distributes the majority of research funds, requires that all research institutions possess an Institutional Review Board (IRB) which establishes and reviews ethical guidelines for medical research. IRBs include both professional and community members, and rule on the ethical acceptability of human research protocols before the research may be started. The IRB makes sure that protocols follow ethical standards and that they do not seek to recruit subjects who might volunteer only out of desperation. (Recently, AIDS advocacy groups have criticized IRBs for not allowing patients to take what might be enormous risks to further research on that lethal disease.) Informed consent forms are also universally mandated by IRBs to document the patient's understanding and acceptance of research conditions. The federal and private institutional bodies described here are usually better at promulgating ethical guidelines than they are at enforcing them. According to ethicist Bernard Lo, ultimately each scientific investigator is most responsible to ensure the enactment of those guidelines. Do medical researchers faithfully comply with the ethical principles outlined above? Most of the time they do. The exceptions usually consist of scientific misconduct in data interpretation or presentation; in other words, they *"fudge the data."*

Do medical researchers sometimes ignore these ethical principles on purpose and thus do harm to their patients? In psychiatric research, this question is often more prominent than in other medical research, perhaps a Cartesian inheritance which makes our minds even more sensitive to us than our bodies. In our experience at McLean Hospital, psychiatric researchers do not knowingly ignore these ethical principles. It can, at times, be challenging to implement them fully, usually because of the unique problems of research in mental illness. For instance, informed consent is often difficult to obtain from a patient during an acute psychotic episode. The most ethical course of conduct would be to obtain permission from a proxy family member or friend. But when mentally ill patients are homeless or without known relatives, then ethics demands that even potentially valuable research has to be foregone. Patients with mental retardation, Alzheimer's disease, and other neuropsychiatric illnesses present similar problems. It is generally accepted that consent by proxy is the optimal solution. Otherwise, no research could be done.

Certainly, the ethics of psychiatric research can be a complicated business. But not all of the complications rest with the researchers. Patients may also have a partial obligation to participate in research. Ethicist Edmund Pellegrino writes that *"the central act of medicine"* is that *"a patient in need who consults a physician wants to know what is wrong, what can be done about it, and what should be done."* What should be done is often the patient's primary concern; but what should be done depends on what is wrong **(diagnosis)** and what can be done **(therapeutics)**. All research, ultimately, is about diagnosis and therapeutics. The ethical basis of medical practice, Pellegrino also asserts, involves a contract between doctor and patient.

Research is sometimes spurred by motivations baser than a desire to help humanity; fame, money, and status can play a significant role. Patients, families, and friends should recognize this fact. They should never, by any means, confer a veritable 'carte blanche trust' upon medical researchers.

The doctor claims competence to diagnose and treat an illness possessed by the patient; he or she needs to follow the principles of beneficence, justice, and autonomy. The patient seeks to help the doctor make the correct diagnosis and give the best treatment; hence he or she, too, has some ethical duties towards the doctor. Among them, Pellegrino notes the duty to be truthful about his or her symptoms, the agreement to seek no more than can be expected from the current state of medical knowledge, and a *"partial obligation to participate in medical research."*

As a member of the human species, the patient has a duty not only to himself, but to other human beings who might have or might develop the same illness. In order to help the doctor make the diagnosis and give the best treatment, the patient must recognize, at least

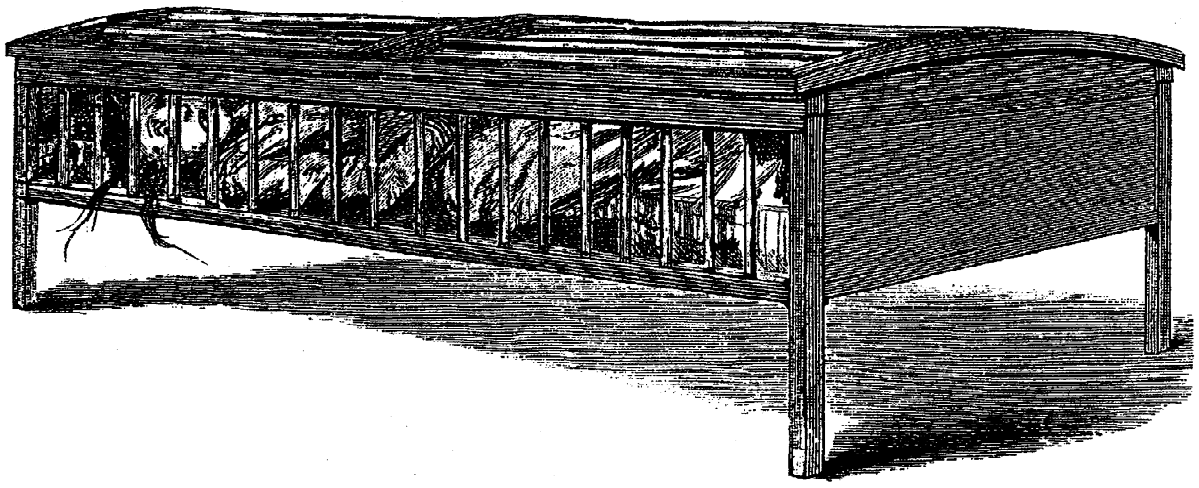
to some degree, his or her duty to participate in research aimed at these issues, even if he or she might not directly benefit from the research.

That does not mean that the patient should put himself or herself in harm's way. Ultimately, the patient and his or her family and friends should try to make a rational decision within the boundaries of their personal preferences and their ethical obligations. So, too, should medical researchers.

Research is sometimes spurred by motivations baser than a desire to help humanity; fame, money, and status can play a significant role. Patients, families, and friends should recognize this fact. They should never, by any means, confer a veritable "carte blanche trust" upon medical researchers.

Inhuman Research is not restricted to Nazi Germany. Dr. Henry Beecher published in 1966 a now famous article on **"Ethics and Human Experimentation"** that provided 22 examples of research in this country that lacked proper informed consent. And it was six years later, in 1972, that the public learned of the U. S. Public Health Service's now infamous study on 400 poor African-Americans in the Tuskegee Institute who were denied Penicillin treatment for syphilis for forty years in order to study the long-term effects of the illness. Congress continues to attempt to compensate the survivors.

Patients, families, and their friends should get to know researchers as human beings first, on that common ethical ground we all share. And researchers need to trust their patients' motivations as well. If both groups recognize that they have ethical obligations to each other, medical research can proceed. Medical research, like medical practice, is a noble and complex endeavor, requiring good will on all sides. As in medical practice, unethical motivations in medical research may cause great harm. Doctors and patients can avert such harm by being aware of and being faithful to the ethics of medical research. ■



DR. BENJAMIN RUSH, "New Techniques of Restraint–THE WOODEN CRIB," 19th Century