Editorials

The Ethics of Clinical Research in the Third World

An essential ethical condition for a randomized clinical trial comparing two treatments for a disease is that there be no good reason for thinking one is better than the other.[1,2] Usually, investigators hope and even expect that the new treatment will be better, but there should not be solid evidence one way or the other. If there is, not only would the trial be scientifically redundant, but the investigators would be guilty of knowingly giving inferior treatment to some participants in the trial. The necessity for investigators to be in this state of equipoise[2] applies to placebo-controlled trials, as well. Only when there is no known effective treatment is it ethical to compare a potential new treatment with a placebo. When effective treatment exists, a placebo may not be used. Instead, subjects in the control group of the study must receive the best known treatment. Investigators are responsible for all subjects enrolled in a trial, not just some of them, and the goals of the research are always secondary to the well-being of the participants. Those requirements are made clear in the Declaration of Helsinki of the World Health Organization (WHO), which is widely regarded as providing the fundamental guiding principles of research involving human subjects.[3] It states, "In research on man [*sic*], the interest of science and society should never take precedence over considerations related to the wellbeing of the subject," and "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."

One reason ethical codes are unequivocal about investigators' primary obligation to care for the human subjects of their research is the strong temptation to subordinate the subjects' welfare to the objectives of the study. That is particularly likely when the research question is extremely important and the answer would probably improve the care of future patients substantially. In those circumstances, it is sometimes argued explicitly that obtaining a rapid, unambiguous answer to the research question is the primary ethical obligation. With the most altruistic of motives, then, researchers may find themselves slipping across a line that prohibits treating human subjects as means to an end. When that line is crossed, there is very little left to protect patients from a callous disregard of their welfare for the sake of research goals. Even informed consent, important though it is, is not protection enough, because of the asymmetry in knowledge and authority between researchers and their subjects. And approval by an institutional review board, though also important, is highly variable in its responsiveness to patients' interests when they conflict with the interests of researchers.

A textbook example of unethical research is the Tuskegee Study of Untreated Syphilis.[4] In that study, which was sponsored by the U.S. Public Health Service and lasted from 1932 to 1972, 412 poor African-American men with untreated syphilis were followed and compared with 204 men free of the disease to determine the natural history of syphilis. Although there was no very good treatment available at the time the study began (heavy metals were the standard treatment), the research continued even after penicillin became widely available and was known to be highly effective against syphilis. The study was not terminated until it came to the attention of a reporter and the outrage provoked by front-page stories in the *Washington Star* and *New York Times* embarrassed the Nixon administration into calling a halt to it.[5] The ethical violations were multiple: Subjects did not provide informed consent (indeed, they were deliberately deceived); they were denied the best known treatment; and the study was continued even after highly effective treatment became available. And what were the arguments in favor of the Tuskegee study? That these poor African-American men probably would not have been treated anyway, so the investigators were merely observing what would have happened if there were no study; and that the study was important (a "never-to-be-repeated opportunity," said one physician after penicillin became available).[6] Ethical concern was even stood on its head when it was suggested that not only was the information valuable, but it was especially so for people like the subjects — an impoverished rural population with a very high rate of untreated syphilis. The only lament seemed to be that many of the subjects inadvertently received treatment by other doctors.

Some of these issues are raised by Lurie and Wolfe elsewhere in this issue of the *Journal*. They discuss the ethics of ongoing trials in the Third World of regimens to prevent the vertical transmission of human immunodeficiency virus (HIV) infection.[7] All except one of the trials employ placebo-treated control groups, despite the fact that zidovudine has already been clearly shown to cut the rate of vertical transmission greatly and is now recommended in the United States for all HIV-infected pregnant women. The justifications are reminiscent of those for the Tuskegee study: Women in the Third World would not receive antiretroviral treatment anyway, so the investigators are simply observing what would happen to the subjects' infants if there were no study. And a placebo-controlled study is the fastest, most efficient way to obtain unambiguous information that will be of greatest value in the Third World. Thus, in response to protests from Wolfe and others to the secretary of Health and Human Services, the directors of the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention

(CDC) — the organizations sponsoring the studies — argued, "It is an unfortunate fact that the current standard of perinatal care for the HIV-infected pregnant women in the sites of the studies does not include any HIV prophylactic intervention at all," and the inclusion of placebo controls "will result in the most rapid, accurate, and reliable answer to the question of the value of the intervention being studied compared to the local standard of care."[8]

Also in this issue of the *Journal*, Whalen et al. report the results of a clinical trial in Uganda of various regimens of prophylaxis against tuberculosis in HIV-infected adults, most of whom had positive tuberculin skin tests.[9] This study, too, employed a placebo-treated control group, and in some ways it is analogous to the studies criticized by Lurie and Wolfe. In the United States it would probably be impossible to carry out such a study, because of long-standing official recommendations that HIV-infected persons with positive tuberculin skin tests receive prophylaxis against tuberculosis. The first was issued in 1990 by the CDC's Advisory Committee for Elimination of Tuberculosis.[10] It stated that tuberculin-test-positive persons with HIV infection "should be considered candidates for preventive therapy." Three years later, the recommendation was reiterated more strongly in a joint statement by the American Thoracic Society and the CDC, in collaboration with the Infectious Diseases Society of America and the American Academy of Pediatrics.[11] According to this statement, ". . . the identification of persons with dual infection and the administration of preventive therapy to these persons is of great importance." However, some believe that these recommendations were premature, since they were based largely on the success of prophylaxis in HIV-negative persons.[12]

Whether the study by Whalen et al. was ethical depends, in my view, entirely on the strength of the preexisting evidence. Only if there was genuine doubt about the benefits of prophylaxis would a placebo group be ethically justified. This is not the place to review the scientific evidence, some of which is discussed in the editorial of Msamanga and Fawzi elsewhere in this issue.[13] Suffice it to say that the case is debatable. Msamanga and Fawzi conclude that "future studies should not include a placebo group, since preventive therapy should be considered the standard of care." I agree. The difficult question is whether there should have been a placebo group in the first place.

Although I believe an argument can be made that a placebo-controlled trial was ethically justifiable because it was still uncertain whether prophylaxis would work, it should not be argued that it was ethical because no prophylaxis is the "local standard of care" in sub-Saharan Africa. For reasons discussed by Lurie and Wolfe, that reasoning is badly flawed.[7] As mentioned earlier, the Declaration of Helsinki requires control groups to receive the "best" current treatment, not the local one. The shift in wording between "best" and "local" may be slight, but the implications are profound. Acceptance of this ethical relativism could result in widespread exploitation of vulnerable Third World populations for research programs that could not be carried out in the sponsoring country.[14] Furthermore, it directly contradicts the Department of Health and Human Services' own regulations governing U.S.-sponsored research in foreign countries,[15] as well as joint guidelines for research in the Third World issued by WHO and the Council for International Organizations of Medical Sciences,[16] which require that human subjects receive protection at least equivalent to that in the sponsoring country. The fact that Whalen et al. offered isoniazid to the placebo group when it was found superior to placebo indicates that they were aware of their responsibility to all the subjects in the trial.

The *Journal* has taken the position that it will not publish reports of unethical research, regardless of their scientific merit.[14,17] After deliberating at length about the study by Whalen at al., the editors concluded that publication was ethically justified, although there remain differences among us. The fact that the subjects gave informed consent and the study was approved by the institutional review board at the University Hospitals of Cleveland and Case Western Reserve University and by the Ugandan National AIDS Research Subcommittee certainly supported our decision but did not allay all our misgivings. It is still important to determine whether clinical studies are consistent with preexisting, widely accepted ethical guidelines, such as the Declaration of Helsinki, and with federal regulations, since they cannot be influenced by pressures specific to a particular study.

Quite apart from the merits of the study by Whalen et al., there is a larger issue. There appears to be a general retreat from the clear principles enunciated in the Nuremberg Code and the Declaration of Helsinki as applied to research in the Third World. Why is that? Is it because the "local standard of care" is different? I don't think so. In my view, that is merely a self-serving justification after the fact. Is it because diseases and their treatments are very different in the Third World, so that information gained in the industrialized world has no relevance and we have to start from scratch? That, too, seems an unlikely explanation, although here again it is often offered as a justification. Sometimes there may be relevant differences between populations, but that cannot be assumed. Unless there are specific indications to the contrary, the safest and most reasonable position is that people everywhere are likely to respond similarly to the same treatment.

I think we have to look elsewhere for the real reasons. One of them may be a slavish adherence to the tenets of clinical trials. According to these, all trials should be randomized, double-blind, and placebo-

controlled, if at all possible. That rigidity may explain the NIH's pressure on Marc Lallemant to include a placebo group in his study, as described by Lurie and Wolfe.[7] Sometimes journals are blamed for the problem, because they are thought to demand strict conformity to the standard methods. That is not true, at least not at this journal. We do not want a scientifically neat study if it is ethically flawed, but like Lurie and Wolfe we believe that in many cases it is possible, with a little ingenuity, to have both scientific and ethical rigor.

The retreat from ethical principles may also be explained by some of the exigencies of doing clinical research in an increasingly regulated and competitive environment. Research in the Third World looks relatively attractive as it becomes better funded and regulations at home become more restrictive. Despite the existence of codes requiring that human subjects receive at least the same protection abroad as at home, they are still honored partly in the breach. The fact remains that many studies are done in the Third World that simply could not be done in the countries sponsoring the work. Clinical trials have become a big business, with many of the same imperatives. To survive, it is necessary to get the work done as quickly as possible, with a minimum of obstacles. When these considerations prevail, it seems as if we have not come very far from Tuskegee after all. Those of us in the research community need to redouble our commitment to the highest ethical standards, no matter where the research is conducted, and sponsoring agencies need to enforce those standards, not undercut them.

MARCIA ANGELL, M.D.

REFERENCES

1. Angell M. Patients' preferences in randomized clinical trials. N Engl J Med 1984;310:1385-7.
2. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987;317:141-5.
3. Declaration of Helsinki IV, 41st World Medical Assembly, Hong Kong, September 1989. In: Annas GJ, Grodin MA, eds. The Nazi doctors and the Nuremberg Code: human rights in human experimentation. New York: Oxford University Press, 1992:339-42.
4. Twenty years after: the legacy of the Tuskegee syphilis study. Hastings Cent Rep 1992;22(6):29-40.
5. Caplan AL. When evil intrudes. Hastings Cent Rep 1992;22(6):29-32.
6. The development of consent requirements in research ethics. In: Faden RR, Beauchamp TL. A history and theory of informed consent. New York: Oxford University Press, 1986:151-99.
7. Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. N Engl J Med 1997;337:853-6.
8. The conduct of clinical trials of maternal–infant transmission of HIV supported by the United States Department of Health and Human Services in developing countries. Washington, D.C.: Department of Health and Human Services, July 1997.
9. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. N Engl J Med 1997;337:801-8.
10. The use of preventive therapy for tuberculous infection in the United States: recommendations of the Advisory Committee for Elimination of Tuberculosis. MMWR Morb Mortal Wkly Rep 1990;39(RR-8):9-12.
11. Bass JB Jr, Farer LS, Hopewell PC, et al. Treatment of tuberculosis and tuberculosis infection in adults and children. Am J Respir Crit Care Med 1994;149:1359-74.
12. De Cock KM, Grant A, Porter JD. Preventive therapy for tuberculosis in HIV-infected persons: international recommendations, research, and practice. Lancet 1995;345:833-6.
13. Msamanga GI, Fawzi WW. The double burden of HIV infection and tuberculosis in sub-Saharan Africa. N Engl J Med 1997;337:849-51.
14. Angell M. Ethical imperialism? Ethics in international collaborative clinical research. N Engl J Med 1988;319:1081-3.
15. Protection of human subjects, 45 CFR § 46 (1996).
16. International ethical guidelines for biomedical research involving human subjects. Geneva: Council for International Organizations of Medical Sciences, 1993.
17. Angell M. The Nazi hypothermia experiments and unethical research today. N Engl J Med 1990;322:1462-4.

THE DOUBLE BURDEN OF HIV INFECTION AND TUBERCULOSIS IN SUB-SAHARAN AFRICA

THE World Health Organization (WHO) estimated that by June 1996 14 million people were living with human immunodeficiency virus (HIV) infection in sub-Saharan Africa. Although it contains only 10 percent of the world's population, sub-Saharan Africa is home to about 65 percent of all the world's HIV-infected people. In several urban centers, more than 10 percent of the asymptomatic adults and about 15 to 30 percent of the women attending prenatal-care clinics are infected. A 1994 paper reported that in rural Uganda more than 80 percent of the deaths among men and women 25 to 44 years of age were attributable to HIV infection.[1] The reported risk of perinatal transmission of HIV is generally higher in African studies (30 to 45 percent) than in European and American studies (7 to 30 percent). Although the median length of time from seroconversion to the appearance of the acquired immunodeficiency syndrome (AIDS) is approximately 10 years in the United States, it is only 4.4 years among female sex workers in Nairobi, Kenya.[2]

The death of one or both parents from HIV infection has left many African children without social, emotional, or economic support. HIV infection has also put additional strains on the already overstretched health care systems. The average annual per capita expenditure on health is $11 for the region, and in several countries it is less than $4. Many areas lack essential drugs and medical supplies, including antibiotics, antiseptics, and gloves. With the increasing privatization of the health care sector, many health services (excluding prenatal care and other prevention programs) are available — but at a price. Although mechanisms have been developed to waive the fees for those who cannot afford them, these may be difficult to implement when the majority of patients are poor. In fact, over 50 percent of the adult patients admitted to the hospital in Africa are infected

with HIV, and many of them are unable to pay for care. Given that HIV infection is most prevalent among the economically productive age groups, patients' families suffer tremendously because of the frequent illnesses and eventual death of those infected.

A secondary epidemic of tuberculosis is accompanying the rise in the number of HIV-infected persons. WHO estimates that worldwide nearly 5 million people are infected with both HIV and tuberculosis, and three quarters of them live in Africa.[3] Prevention of tuberculosis among those with HIV infection is a logical public health goal, given that such patients are at high risk for tuberculosis, which in turn is associated with an increased likelihood of death. Long before the advent of AIDS, preventive therapy with isoniazid was shown to reduce the occurrence of tuberculosis significantly among contacts of patients with active disease and among those with conversion of a tuberculin skin test to positive.[4] Because of concern about the increased adverse effects of antituberculosis therapy in HIV-positive patients, a number of trials have examined the safety and efficacy of chemoprophylaxis in this population. Placebo-controlled studies were carried out in Haiti, Zambia, and Kenya with varying designs and results. In the Haitian study, a 12-month course of isoniazid significantly reduced the incidence of tuberculosis among HIV-positive subjects with positive tuberculin skin tests. However, about 40 percent of the new cases were based on presumptive diagnoses of tuberculosis.[5] In the Zambian study, a six-month course of isoniazid reduced the incidence of tuberculosis among patients with positive tuberculin skin tests.[6] But in the study from Kenya there was no effect of six months of therapy with isoniazid among HIV-positive subjects, although the number who had positive tuberculin skin tests was too small to permit the effect of therapy to be examined in this subgroup.[7]

In this issue of the *Journal,* Whalen et al. report that a six-month course of isoniazid among HIV-infected Ugandans with positive tuberculin skin tests reduced the risk of tuberculosis by about 70 percent after a mean follow-up period of 15 months.[8] Isoniazid therapy may have reduced the risk of tuberculosis among subjects with anergy as well. This study also adds to our knowledge of the role of preventive therapies that include drugs other than isoniazid, such as rifampin and pyrazinamide. For the subjects who received a three-month course of isoniazid and rifampin, there was about a 60 percent reduction in the risk of tuberculosis as compared with those given placebo. The reduction in the risk of tuberculosis for those given isoniazid, rifampin, and pyrazinamide was 49 percent. Alternative regimens are needed for those infected with isoniazid-resistant strains, and the shorter courses are likely to improve compliance. However, they are also associated with a higher risk of adverse events and are most costly. Although none of the treatments in this study reduced mortality significantly, the sample size and duration of follow-up were inadequate for this question to be examined.

The results of the study from Uganda support the administration of isoniazid as preventive therapy for persons in sub-Saharan Africa who are infected with HIV and have positive tuberculin skin tests. Before any such program can be implemented on a communitywide level, research on the operational and programmatic questions is urgently needed. Is preventive therapy feasible in sub-Saharan Africa? Is it cost effective, as compared with other uses of scarce health care dollars? The introduction of a program of preventive therapy requires human resources, laboratory supplies, drugs, and transport facilities in order to carry out voluntary counseling and testing for HIV infection, to identify and exclude all those with active tuberculosis, to perform tuberculin skin testing, and to provide follow-up care. The exclusion of those with active tuberculosis is important, since treatment with isoniazid alone is insufficient and would lead to the development of drug-resistant organisms. It is also important to exclude people with liver problems at base line and to terminate therapy among those in whom hepatotoxicity develops during follow-up. In one report, unsupervised preventive therapy in Uganda was associated with poor compliance.[9] On the other hand, directly observed therapy for tuberculosis given by nonmedical staff was reported to be successful in a South African community,[10] and a similar system could be instituted for preventive therapy.

A number of scientific issues still need to be addressed. These include the question of how long the protection afforded by preventive therapy lasts. The protection afforded by 6 to 12 months of isoniazid therapy is probably lifelong in the parts of the world where the risk of transmission of tuberculosis is low. In sub-Saharan Africa, however, the duration of efficacy may be much shorter because the risk of infection or reinfection is so high. The efficacy and economics of providing long-term preventive therapy or lifelong therapy and the risk of accelerating drug resistance need to be examined.[11] Given our current state of knowledge, however, future studies should not include a placebo group, since preventive therapy should be considered the standard of care.

In sub-Saharan Africa, where there is little access to antiretroviral drugs, preventive therapy for tuberculosis may be the single most affordable intervention for the prolongation of a healthy life in HIV-infected persons. By preventing tuberculosis, these regimens will also help reduce the transmission of tuberculosis in African communities. Although we agree with WHO that interrupting the transmission of tuberculosis by curative treatment of infectious cases should continue to be the priority for tuberculosis programs,[12] efforts need to be made to apply these important findings about preventive therapy to the community and the region where the study was

carried out. It is clear that African programs of tuberculosis and AIDS control will be unable to undertake this additional responsibility alone, since they rely largely on donor support. Extension of these programs will be possible only through the cooperation of many governments, pharmaceutical companies, and international agencies.

GERNARD I. MSAMANGA, M.D., SC.D.
Muhimbili Medical Center
Dar es Salaam, Tanzania

WAFAIE W. FAWZI, M.B., B.S., DR.P.H.
Harvard School of Public Health
Boston, MA 02115

REFERENCES

1. Mulder DW, Nunn AJ, Kamali A, Nakiyingi J, Wagner HU, Kengeya-Kayondo JF. Two-year HIV-1-associated mortality in a Ugandan rural population. Lancet 1994;343:1021-3.
2. Anzala OA, Nagelkerke NJ, Bwayo JJ, et al. Rapid progression to disease in African sex workers with human immunodeficiency virus type 1 infection. J Infect Dis 1995;171:686-9. [Erratum, J Infect Dis 1996;173:1529.]
3. The HIV/AIDS and tuberculosis epidemics: implications for TB control. Geneva: World Health Organization, 1994. (WHO/TB/CARG(4)/94.4.)
4. O'Brien RJ. Preventive therapy for tuberculosis. In: Porter JDH, McAdam KPWJ, eds. Tuberculosis: back to the future. Chichester, England: Wiley, 1994:151-66.
5. Pape JW, Jean SS, Ho JL, Hafner A, Johnson WD Jr. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. Lancet 1993;342:268-72.
6. Wadhawan D, Hira S, Mwansa N, Perine P. Preventive tuberculosis chemotherapy with isoniazid among persons infected with HIV-1. Presented at the Eighth International Conference on AIDS/Third STD World Congress, Amsterdam, July 19–24, 1992. abstract.
7. Hawken MP, Meme HK, Elliott LC, et al. Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trial. AIDS 1997;11:875-82.
8. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. N Engl J Med 1997;337:801-8.
9. Aisu T, Raviglione MC, van Praag E, et al. Preventive chemotherapy for HIV-associated tuberculosis in Uganda: an operational assessment at a voluntary counselling and testing centre. AIDS 1995;9:267-73.
10. Wilkinson D, Davies GR, Connolly C. Directly observed therapy for tuberculosis in rural South Africa, 1991 through 1994. Am J Public Health 1996;86:1094-7.
11. De Cock KM, Grant A, Porter JD. Preventive therapy for tuberculosis in HIV-infected persons: international recommendations, research, and practice. Lancet 1995;345:833-6.
12. Tuberculosis preventive therapy in HIV-infected individuals. Wkly Epidemiol Rec 1993;68:361-4.

PHARMACOLOGIC ADVANCES IN THE TREATMENT OF SCHIZOPHRENIA

ALTHOUGH medications have dramatically improved the lives of many people with schizophrenia, treatment resistance remains a serious problem. Three quarters of patients with schizophrenia become ill before the age of 25. The manifestations of the disease include two types of symptoms — "positive" and "negative." Positive symptoms are distortions of normal functioning. Distortion of perceptions may appear as hallucinations; distortion of inferential thinking may lead to delusions. Negative symptoms involve the loss of normal functioning — the loss of will, range of affect, pleasure, and fluency and content of speech. The intensity of these symptoms and the residual disability they cause may prevent people with schizophrenia from beginning a career, completing an education, or enjoying a life that may once have been filled with great promise. Rates of employment among people with schizophrenia rarely exceed 20 percent.

Schizophrenia is a chronic illness; less than 20 percent of patients recover from a single episode of psychosis and return to the lives they knew before. More frequently, patients have repeated episodes, with decrements in base-line functioning accompanying each one; a few never recover from the first episode and continue to have pervasive psychotic symptoms.

For 35 years, the pharmacologic approach to schizophrenia involved antipsychotic medication based on D2 dopamine-receptor antagonism. The dopamine hypothesis of schizophrenia was proposed in 1963,[1] 10 years after the first antipsychotic medication was introduced. This hypothesis was based on the observation that all antipsychotic drugs had a strong affinity for a particular dopamine receptor (D2) and that dopamine agonists, such as methylphenidate and dextroamphetamine, could produce a psychotic condition. Standard antipsychotic drugs differed only in their side effects, not in their mechanisms of action. Consistent side effects were those associated with D2 antagonism, most likely in the nigrostriatal dopamine tracts, which led to extrapyramidal symptoms of stiffness, tremor, pseudoparkinsonism, and akathisia. Subjectively, these side effects were unpleasant, leading to cycles of noncompliance and relapse. Estimates of 40 percent rates of noncompliance among patients treated with antipsychotic agents were not unusual; when noncompliance was combined with the therapeutic limitations of the drugs, rates of relapse were quite high.

Clozapine, the first novel antipsychotic drug to appear, was introduced in the United States in 1989. A conventional antipsychotic drug, such as haloperidol, produced its antipsychotic effects after binding to 80 percent of dopamine D2 receptors; clozapine produced an antipsychotic effect after binding to less than 20 percent of D2 receptors. Hypotheses about clozapine's principal mechanism of action have been hotly debated, but without resolution. Proposed mechanisms of action have focused, separately and in combination, on other dopamine receptors (D1 and D4) and on clozapine's effects on the serotonin receptor 5-hydroxytryptamine. The initial interest in serotonin receptors was stimulated by lysergic acid diethylamide (LSD), which has high serotonergic activity. Until clozapine was developed, however, investigation of serotonin receptors in the context of schizophrenia had fallen off. This was because the main psychotic symptoms associated with

LSD are visual hallucinations, which are uncommon in schizophrenia, rather than the auditory hallucinations that predominate in the disease.

The introduction of clozapine was delayed by its clear association with agranulocytosis in approximately 1 percent of those receiving it and by the deaths of a number of patients in Europe. Thus, the requirements of the Food and Drug Administration (FDA) for clozapine were quite stringent. The agency required a demonstration of efficacy in patients whose disease was refractory to treatment with standard antipsychotic drugs. No other antipsychotic drug had ever been required to meet such a standard. Furthermore, an elaborate system of monitoring patients was required, including weekly venipuncture for assessment of white-cell counts. Despite its risks, clozapine was an exciting medication because it produced results in patients who had not previously responded to treatment, without producing extrapyramidal side effects. It was expensive, however, in terms of both its cost — about $6,000 a year at my institution — and the additional cost of the weekly blood monitoring — about $1,000 a year. In this era of cost accountability, the use of clozapine was often stringently restricted in hospital and managed-care formularies. Moreover, the main study of this drug focused on only a six-week period and did not examine costs.[2]

In this issue of the *Journal*, Rosenheck et al. report on their comparison of the efficacy of haloperidol and clozapine in a group of schizophrenic patients with moderately severe illness who were treated at Veterans Affairs medical centers.[3] The results in terms of efficacy are certainly interesting on their own: clozapine was shown to have a small but important clinical advantage over haloperidol. However, two additional findings are potentially even more important. First, patients showed their dislike of the side effects of haloperidol by ceasing to take it. Second, the study evaluated treatment for 12 months, a sufficient time for Rosenheck et al. to use information on costs to demonstrate that, despite substantially higher costs for the medication, the total costs for a year of treatment with clozapine and a year of treatment with haloperidol were similar. Patients taking clozapine required fewer days in the hospital and more outpatient visits for treatment. Because of the high cost of hospitalization (at least $500 a day), the reduced number of hospital days offset the increased costs of medication and outpatient expenses associated with clozapine.

Clozapine has been a good drug, but it is far from perfect. Its association with agranulocytosis and a small but important risk of death has increased the demand for new drugs that will perform equally well, but without the life-threatening side effects. Two new antipsychotic drugs, risperidone and olanzapine, have been introduced in the United States during the past several years, and a third, sertindole, is expected to be released shortly. These drugs are all associated with a low risk of extrapyramidal side effects in their recommended dosage range. They do not cause agranulocytosis. But it is uncertain whether they are equivalent to clozapine in terms of efficacy in patients whose illness is otherwise refractory to treatment, and whether their use is associated with lower rates of hospitalization than that of standard antipsychotic drugs.

Risperidone, olanzapine, and sertindole faced a different standard for FDA approval from clozapine; efficacy in treating patients with refractory disease did not have to be demonstrated. In comparisons with a placebo and with a standard antipsychotic drug — namely, haloperidol[4-6] — all were superior to placebo. Their relative efficacy as compared with haloperidol in short-term studies is a matter of debate among observers who interpret the findings in a variety of ways. Nonetheless, all have demonstrated efficacy in treating acute psychosis due to schizophrenia. Their purported mechanisms of action differ. Olanzapine has an affinity for multiple receptors, similar to that of clozapine; risperidone and sertindole have principal affinities for components of the serotonin system. All produce far fewer extrapyramidal symptoms than haloperidol and less of the subjective distress associated with such symptoms, and they should therefore be better accepted by patients. Greater acceptance and improved compliance may, in turn, be associated with increased efficacy.

To ensure a position on hospital and managed-care formularies for any new drug for schizophrenia that has a higher price than the standard drugs, it will need to be shown that the expense is offset by savings in the costs of hospital care or other costs. The study of clozapine by Rosenheck et al. should encourage comparably rigorous evaluations of other drugs.

SAMUEL J. KEITH, M.D.
University of New Mexico School of Medicine
Albuquerque, NM 87131-5326

REFERENCES

1. Carlsson A, Lindqvist M. Effect of chlorpromazine and haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta Pharmacol Toxicol 1963;20:140-4.
2. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789-96.
3. Rosenheck R, Cramer J, Xu W, et al. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. N Engl J Med 1997;337:809-15.
4. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825-35.
5. Beasley CM Jr, Tollefson G, Tran P, Satterlee W, Sanger T, Hamilton S. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996;14:111-23.
6. Zimbroff DL, Kane JM, Tamminga CA, et al. Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. Am J Psychiatry 1997;154:782-91.

Sounding Board

Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries

IT has been almost three years since the *Journal*[1] published the results of AIDS Clinical Trials Group (ACTG) Study 076, the first randomized, controlled trial in which an intervention was proved to reduce the incidence of human immunodeficiency virus (HIV) infection. The antiretroviral drug zidovudine, administered orally to HIV-positive pregnant women in the United States and France, administered intravenously during labor, and subsequently administered to the newborn infants, reduced the incidence of HIV infection by two thirds.[2] The regimen can save the life of one of every seven infants born to HIV-infected women.

Because of these findings, the study was terminated at the first interim analysis and within two months after the results had been announced, the Public Health Service had convened a meeting and concluded that the ACTG 076 regimen should be recommended for all HIV-positive pregnant women without substantial prior exposure to zidovudine and should be considered for other HIV-positive pregnant women on a case-by-case basis.[3] The standard of care for HIV-positive pregnant women thus became the ACTG 076 regimen.

In the United States, three recent studies of clinical practice report that the use of the ACTG 076 regimen is associated with decreases of 50 percent or more in perinatal HIV transmission.[4-6] But in developing countries, especially in Asia and sub-Saharan Africa, where it is projected that by the year 2000, 6 million pregnant women will be infected with HIV,[7] the potential of the ACTG 076 regimen remains unrealized primarily because of the drug's exorbitant cost in most countries.

Clearly, a regimen that is less expensive than ACTG 076 but as effective is desirable, in both developing and industrialized countries. But there has been uncertainty about what research design to use in the search for a less expensive regimen. In June 1994, the World Health Organization (WHO) convened a group in Geneva to assess the agenda for research on perinatal HIV transmission in the wake of ACTG 076. The group, which included no ethicists, concluded, "Placebo-controlled trials offer the best option for a rapid and scientifically valid assessment of alternative antiretroviral drug regimens to prevent [perinatal] transmission of HIV."[8] This unpublished document has been widely cited as justification for subsequent trials in developing countries. In our view, most of these trials are unethical and will lead to hundreds of preventable HIV infections in infants.

Primarily on the basis of documents obtained from the Centers for Disease Control and Prevention (CDC), we have identified 18 randomized, controlled trials of interventions to prevent perinatal HIV transmission that either began to enroll patients after the ACTG 076 study was completed or have not yet begun to enroll patients. The studies are designed to evaluate a variety of interventions: antiretroviral drugs such as zidovudine (usually in regimens that are less expensive or complex than the ACTG 076 regimen), vitamin A and its derivatives, intrapartum vaginal washing, and HIV immune globulin, a form of immunotherapy. These trials involve a total of more than 17,000 women.

In the two studies being performed in the United States, the patients in all the study groups have unrestricted access to zidovudine or other antiretroviral drugs. In 15 of the 16 trials in developing countries, however, some or all of the patients are not provided with antiretroviral drugs. Nine of the 15 studies being conducted outside the United States are funded by the U.S. government through the CDC or the National Institutes of Health (NIH), 5 are funded by other governments, and 1 is funded by the United Nations AIDS Program. The studies are being conducted in Côte d'Ivoire, Uganda, Tanzania, South Africa, Malawi, Thailand, Ethiopia, Burkina Faso, Zimbabwe, Kenya, and the Dominican Republic. These 15 studies clearly violate recent guidelines designed specifically to address ethical issues pertaining to studies in developing countries. According to these guidelines, "The ethical standards applied should be no less exacting than they would be in the case of research carried out in [the sponsoring] country."[9] In addition, U.S. regulations governing studies performed with federal funds domestically or abroad specify that research procedures must "not unnecessarily expose subjects to risk."[10]

The 16th study is noteworthy both as a model of an ethically conducted study attempting to identify less expensive antiretroviral regimens and as an indication of how strong the placebo-controlled trial orthodoxy is. In 1994, Marc Lallemant, a researcher at the Harvard School of Public Health, applied for NIH funding for an equivalency study in Thailand in which three shorter zidovudine regimens were to be compared with a regimen similar to that used in the ACTG 076 study. An equivalency study is typically conducted when a particular regimen has already been proved effective and one is interested in determining whether a second regimen is about as effective but less toxic or expensive.[11] The NIH study section repeatedly put pressure on Lallemant and the Harvard School of Public Health to conduct a

placebo-controlled trial instead, prompting the director of Harvard's human subjects committee to reply, "The conduct of a placebo-controlled trial for [zidovudine] in pregnant women in Thailand would be unethical and unacceptable, since an active-controlled trial is feasible."[12] The NIH eventually relented, and the study is now under way. Since the nine studies of antiretroviral drugs have attracted the most attention, we focus on them in this article.

ASKING THE WRONG RESEARCH QUESTION

There are numerous areas of agreement between those conducting or defending these placebo-controlled studies in developing countries and those opposing such trials. The two sides agree that perinatal HIV transmission is a grave problem meriting concerted international attention; that the ACTG 076 trial was a major breakthrough in perinatal HIV prevention; that there is a role for research on this topic in developing countries; that identifying less expensive, similarly effective interventions would be of enormous benefit, given the limited resources for medical care in most developing countries; and that randomized studies can help identify such interventions.

The sole point of disagreement is the best comparison group to use in assessing the effectiveness of less-expensive interventions once an effective intervention has been identified. The researchers conducting the placebo-controlled trials assert that such trials represent the only appropriate research design, implying that they answer the question, "Is the shorter regimen better than nothing?" We take the more optimistic view that, given the findings of ACTG 076 and other clinical information, researchers are quite capable of designing a shorter antiretroviral regimen that is approximately as effective as the ACTG 076 regimen. The proposal for the Harvard study in Thailand states the research question clearly: "Can we reduce the duration of prophylactic [zidovudine] treatment without increasing the risk of perinatal transmission of HIV, that is, without compromising the demonstrated efficacy of the standard ACTG 076 [zidovudine] regimen?"[13] We believe that such equivalency studies of alternative antiretroviral regimens will provide even more useful results than placebo-controlled trials, without the deaths of hundreds of newborns that are inevitable if placebo groups are used.

At a recent congressional hearing on research ethics, NIH director Harold Varmus was asked how the Department of Health and Human Services could be funding both a placebo-controlled trial (through the CDC) and a non–placebo-controlled equivalency study (through the NIH) in Thailand. Dr. Varmus conceded that placebo-controlled studies are "not the only way to achieve results."[14] If the research can be satisfactorily conducted in more than one way, why not select the approach that minimizes loss of life?

INADEQUATE ANALYSIS OF DATA FROM ACTG 076 AND OTHER SOURCES

The NIH, CDC, WHO, and the researchers conducting the studies we consider unethical argue that differences in the duration and route of administration of antiretroviral agents in the shorter regimens, as compared with the ACTG 076 regimen, justify the use of a placebo group.[15-18] Given that ACTG 076 was a well-conducted, randomized, controlled trial, it is disturbing that the rich data available from the study were not adequately used by the group assembled by WHO in June 1994, which recommended placebo-controlled trials after ACTG 076, or by the investigators of the 15 studies we consider unethical.

In fact, the ACTG 076 investigators conducted a subgroup analysis to identify an appropriate period for prepartum administration of zidovudine. The approximate median duration of prepartum treatment was 12 weeks. In a comparison of treatment for 12 weeks or less (average, 7) with treatment for more than 12 weeks (average, 17), there was no univariate association between the duration of treatment and its effect in reducing perinatal HIV transmission ($P = 0.99$) (Gelber R: personal communication). This analysis is somewhat limited by the number of infected infants and its post hoc nature. However, when combined with information such as the fact that in non–breast-feeding populations an estimated 65 percent of cases of perinatal HIV infection are transmitted during delivery and 95 percent of the remaining cases are transmitted within two months of delivery,[19] the analysis *suggests* that the shorter regimens may be equally effective. This finding should have been explored in later studies by randomly assigning women to longer or shorter treatment regimens.

What about the argument that the use of the oral route for intrapartum administration of zidovudine in the present trials (as opposed to the intravenous route in ACTG 076) justifies the use of a placebo? In its protocols for its two studies in Thailand and Côte d'Ivoire, the CDC acknowledged that previous "pharmacokinetic modelling data suggest that [zidovudine] serum levels obtained with this [oral] dose will be similar to levels obtained with an intravenous infusion."[20]

Thus, on the basis of the ACTG 076 data, knowledge about the timing of perinatal transmission, and pharmacokinetic data, the researchers should have had every reason to believe that well-designed shorter regimens would be more effective than placebo. These findings seriously disturb the equipoise (uncertainty over the likely study result) necessary to justify a placebo-controlled trial on ethical grounds.[21]

DEFINING PLACEBO AS THE STANDARD OF CARE IN DEVELOPING COUNTRIES

Some officials and researchers have defended the use of placebo-controlled studies in developing coun-

tries by arguing that the subjects are treated at least according to the standard of care in these countries, which consists of unproven regimens or no treatment at all. This assertion reveals a fundamental misunderstanding of the concept of the standard of care. In developing countries, the standard of care (in this case, not providing zidovudine to HIV-positive pregnant women) is not based on a consideration of alternative treatments or previous clinical data, but is instead an economically determined policy of governments that cannot afford the prices set by drug companies. We agree with the Council for International Organizations of Medical Sciences that researchers working in developing countries have an ethical responsibility to provide treatment that conforms to the standard of care in the sponsoring country, when possible.[9] An exception would be a standard of care that required an exorbitant expenditure, such as the cost of building a coronary care unit. Since zidovudine is usually made available free of charge by the manufacturer for use in clinical trials, excessive cost is not a factor in this case. Acceptance of a standard of care that does not conform to the standard in the sponsoring country results in a double standard in research. Such a double standard, which permits research designs that are unacceptable in the sponsoring country, creates an incentive to use as research subjects those with the least access to health care.

What are the potential implications of accepting such a double standard? Researchers might inject live malaria parasites into HIV-positive subjects in China in order to study the effect on the progression of HIV infection, even though the study protocol had been rejected in the United States and Mexico. Or researchers might randomly assign malnourished San (bushmen) to receive vitamin-fortified or standard bread. One might also justify trials of HIV vaccines in which the subjects were not provided with condoms or state-of-the-art counseling about safe sex by arguing that they are not customarily provided in the developing countries in question. These are not simply hypothetical worst-case scenarios; the first two studies have already been performed,[22,23] and the third has been proposed and criticized.[24]

Annas and Grodin recently commented on the characterization and justification of placebos as a standard of care: "'Nothing' is a description of what happens; 'standard of care' is a normative standard of effective medical treatment, whether or not it is provided to a particular community."[25]

JUSTIFYING PLACEBO-CONTROLLED TRIALS BY CLAIMING THEY ARE MORE RAPID

Researchers have also sought to justify placebo-controlled trials by arguing that they require fewer subjects than equivalency studies and can therefore be completed more rapidly. Because equivalency studies are simply concerned with excluding alternative interventions that fall below some preestablished level of efficacy (as opposed to establishing which intervention is superior), it is customary to use one-sided statistical testing in such studies.[11] The numbers of women needed for a placebo-controlled trial and an equivalency study are similar.[26] In a placebo-controlled trial of a short course of zidovudine, with rates of perinatal HIV transmission of 25 percent in the placebo group and 15 percent in the zidovudine group, an alpha level of 0.05 (two-sided), and a beta level of 0.2, 500 subjects would be needed. An equivalency study with a transmission rate of 10 percent in the group receiving the ACTG 076 regimen, a difference in efficacy of 6 percent (above the 10 percent), an alpha level of 0.05 (one-sided), and a beta level of 0.2 would require 620 subjects (McCarthy W: personal communication).

TOWARD A SINGLE INTERNATIONAL STANDARD OF ETHICAL RESEARCH

Researchers assume greater ethical responsibilities when they enroll subjects in clinical studies, a precept acknowledged by Varmus recently when he insisted that all subjects in an NIH-sponsored needle-exchange trial be offered hepatitis B vaccine.[27] Residents of impoverished, postcolonial countries, the majority of whom are people of color, must be protected from potential exploitation in research. Otherwise, the abominable state of health care in these countries can be used to justify studies that could never pass ethical muster in the sponsoring country.

With the increasing globalization of trade, government research dollars becoming scarce, and more attention being paid to the hazards posed by "emerging infections" to the residents of industrialized countries, it is likely that studies in developing countries will increase. It is time to develop standards of research that preclude the kinds of double standards evident in these trials. In an editorial published nine years ago in the *Journal,* Marcia Angell stated, "Human subjects in any part of the world should be protected by an irreducible set of ethical standards."[28] Tragically, for the hundreds of infants who have needlessly contracted HIV infection in the perinatal-transmission studies that have already been completed, any such protection will have come too late.

PETER LURIE, M.D., M.P.H.
SIDNEY M. WOLFE, M.D.
Public Citizen's Health Research Group
Washington, DC 20009

REFERENCES

1. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal–infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994;331:1173-80.

2. Sperling RS, Shapiro DE, Coombs RW, et al. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. N Engl J Med 1996;335:1621-9.
3. Recommendations of the U.S. Public Health Service Task Force on the use of zidovudine to reduce perinatal transmission of human immunodeficiency virus. MMWR Morb Mortal Wkly Rep 1994;43(RR-11):1-20.
4. Fiscus SA, Adimora AA, Schoenbach VJ, et al. Perinatal HIV infection and the effect of zidovudine therapy on transmission in rural and urban counties. JAMA 1996;275:1483-8.
5. Cooper E, Diaz C, Pitt J, et al. Impact of ACTG 076: use of zidovudine during pregnancy and changes in the rate of HIV vertical transmission. In: Program and abstracts of the Third Conference on Retroviruses and Opportunistic Infections, Washington, D.C., January 28–February 1, 1996. Washington, D.C.: Infectious Diseases Society of America, 1996:57.
6. Simonds RJ, Nesheim S, Matheson P, et al. Declining mother to child HIV transmission following perinatal ZDV recommendations. Presented at the 11th International Conference on AIDS, Vancouver, Canada, July 7–12, 1996. abstract.
7. Scarlatti G. Paediatric HIV infection. Lancet 1996;348:863-8.
8. Recommendations from the meeting on mother-to-infant transmission of HIV by use of antiretrovirals, Geneva, World Health Organization, June 23–25, 1994.
9. World Health Organization. International ethical guidelines for biomedical research involving human subjects. Geneva: Council for International Organizations of Medical Sciences, 1993.
10. 45 CFR 46.111(a)(1).
11. Testing equivalence of two binomial proportions. In: Machin D, Campbell MJ. Statistical tables for the design of clinical trials. Oxford, England: Blackwell Scientific, 1987:35-53.
12. Brennan TA. Letter to Gilbert Meier, NIH Division of Research Ethics, December 28, 1994.
13. Lallemant M, Vithayasai V. A short ZDV course to prevent perinatal HIV in Thailand. Boston: Harvard School of Public Health, April 28, 1995.
14. Varmus H. Testimony before the Subcommittee on Human Resources, Committee on Government Reform and Oversight, U.S. House of Representatives, May 8, 1997.
15. Draft talking points: responding to Public Citizen press conference. Press release of the National Institutes of Health, April 22, 1997.
16. Questions and answers: CDC studies of AZT to prevent mother-to-child HIV transmission in developing countries. Press release of the Centers for Disease Control and Prevention, Atlanta. (undated document.)
17. Questions and answers on the UNAIDS sponsored trials for the prevention of mother-to-child transmission: background brief to assist in responding to issues raised by the public and the media. Press release of the United Nations AIDS Program. (undated document.)
18. Halsey NA, Meinert CL, Ruff AJ, et al. Letter to Harold Varmus, Director of National Institutes of Health. Baltimore: Johns Hopkins University, May 6, 1997.
19. Wiktor SZ, Ehounou E. A randomized placebo-controlled intervention study to evaluate the safety and effectiveness of oral zidovudine administered in late pregnancy to reduce the incidence of mother-to-child transmission of HIV-1 in Abidjan, Cote D'Ivoire. Atlanta: Centers for Disease Control and Prevention. (undated document.)
20. Rouzioux C, Costagliola D, Burgard M, et al. Timing of mother-to-child HIV-1 transmission depends on maternal status. AIDS 1993;7:Suppl 2:S49-S52.
21. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987;317:141-5.
22. Heimlich HJ, Chen XP, Xiao BQ, et al. CD4 response in HIV-positive patients treated with malaria therapy. Presented at the 11th International Conference on AIDS, Vancouver, B.C., July 7–12, 1996. abstract.
23. Bishop WB, Laubscher I, Labadarios D, Rehder P, Louw ME, Fellingham SA. Effect of vitamin-enriched bread on the vitamin status of an isolated rural community — a controlled clinical trial. S Afr Med J 1996;86: Suppl:458-62.
24. Lurie P, Bishaw M, Chesney MA, et al. Ethical, behavioral, and social aspects of HIV vaccine trials in developing countries. JAMA 1994;271: 295-301.
25. Annas G, Grodin M. An apology is not enough. Boston Globe. May 18, 1997:C1-C2.
26. Freedman B, Weijer C, Glass KC. Placebo orthodoxy in clinical research. I. Empirical and methodological myths. J Law Med Ethics 1996; 24:243-51.
27. Varmus H. Comments at the meeting of the Advisory Committee to the Director of the National Institutes of Health, December 12, 1996.
28. Angell M. Ethical imperialism? Ethics in international collaborative clinical research. N Engl J Med 1988;319:1081-3.