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The worldwide demand for relevance in health research raises old ethical issues that require new solutions. The paper by Willett, Kilama and Kihamia on "*Ascaris* and Growth Rates: A Randomized Trial of Treatment,"[1] in this issue of the Journal, raises questions that will be of increasing concern in the evolving climate of international collaborative research, especially in relation to drugs which might be used in mass public health programs. A whole new range of parameters needs to be included in testing standards going beyond the usual considerations of safety and effectiveness. These include cost, acceptability, efficiency in alternative delivery systems, and the range of criteria identified with the term "appropriate technology."

Tensions are becoming more acute internationally because U.S. ethical standards for research are not necessarily congruent with national customs and practices around the world. The World Health Organization is attempting to play a leadership role in defining international standards, especially through its Special Programs for Research in Human Reproduction and in Tropical Diseases.[2,3] The Global and Regional Advisory Committees on Research provide a forum for discussing and stimulating new ideas. More focused definition of issues is necessary to clarify future relationships and move beyond current cliches.

In most developing countries, international research has acquired a bad reputation in recent years. There were all too many instances which could be interpreted as exploitive. The general charge has been that poor populations in developing countries were being used as guinea pigs and that some of the studies done would not have been permitted in institutions of developed countries. Even more ubiquitous were accusations that scientists from developed countries engaged in "bleed and fly" studies which used local scientists but gave them no credit. These criticisms resulted in a vociferous backlash against academic colonialism which peaked about ten years ago. Fortunately, the old arrogant style of U.S. dominated research overseas is no longer permitted by host countries or encouraged by funding agencies.

A new era of mutual collaboration seems to presage a more healthy continuing relationship in the search of new knowledge. In most developing countries there are now highly qualified scientists who can bring special knowledge and understanding into any collaborative relationship. National collaborators can arrange administrative and political clearances, provide an institutional base, arrange access to populations in the field or in clinical facilities, provide understanding of local culture and ecology, and, most importantly, ensure relevance to local needs. The international colleague can bring in expertise, funds, technology, and understanding that comes from comparative research and the important objectivity of being able to stand outside of local cultural and administrative patterns to perceive new associations and insights. The contributions of the local national collaborator are so important that decisions about priority in authorship need to include much more than who conceptualized the research and did the actual writing.

International collaborative research should produce results that are of mutual advantage. No research should be undertaken unless benefit accrues to those being

studied. For international collaborators there is the great advantage that new generalizations and understanding can emerge because of the different experimental conditions in an international setting, especially from comparative studies.

The research reported here by Willet, et al, fits well with most aspects of the new orientation toward collaborative research. The important role of local colleagues in field activities is recognized by their inclusion as coauthors. The balance between roles of participants was clearly and carefully worked out.

Most commendable is the impression that the research was done in such a way as to contribute directly to decisions about health needs and programs in Tanzania. The question studied emerged from an understanding of the relative importance of local problems with findings being interpreted mainly in terms of relevance to eventual mass implementation in public health programs. Practical measures were defined and cost calculations were made which indicated that the measures defined could be implemented in a mass national program.

In an area where moderate ascariasis and malnutrition were common, the researchers were able to measure the benefits of reducing worm burden in improving nutritional status of preschool children. The experimental design seems to have been carefully planned and implemented with selection of treatment and control groups by random numbers, double blind measurements and careful statistical analysis. At the end of a year's observation of 273 preschool children, the group receiving trimonthly levamisole treatment had 8 per cent greater weight gain than placebo-treated controls ($p = .06$). Results were more specific in 78 children known to have been infected with ascaris at the beginning with 21 per cent greater weight gain ($p = .03$). A good discussion of what is known about physiological mechanisms provides a reasonable rationale explaining how worms might directly consume nutrients, and also how moderate malabsorption might be produced by changes in intestinal villi.

This study is an important contribution to the further understanding of the synergism between infections and malnutrition, as previously discussed by Scrimshaw, et al.[4] It provides a sound scientific basis for several suggestive studies that had been done in India and Kenya but without this scientific precision. It suggests that regular periodic mass treatment with a nontoxic ascaricide in groups of children with mass infestation could be a simple and effective means of promoting better nutritional status. This community treatment could be based not on individual diagnosis but on community diagnosis based on epidemiological definition of infection rates.

The main question raised by the research is the ethical concern that it was deemed impossible to get written informed consent from parents.* A letter from the Director General of Health Services for Tanzania relating to a follow-up study states, "As you know, we do not in this country require written consent of human subjects involved in this type of study. We have nevertheless examined the research proposal and do not see any substantial risk to the subjects. As you have shown in your study, ascariasis is hyperandemic in Lushoto and unfortunately many children have to live with it. The drugs you will be using are widely distributed. In Tanzania, they are even available in shops in very remote areas." The Peter Bent Brigham Hospital's Human Subjects Committee reviewed and approved the proposal which included the statement, "Individual informed consent is not a tradition or a requirement in Tanzanian medical research, and is not a practical possibility in this study." Later the application says,

> "In the villages in which the study is to be conducted, leaders and individuals will be told that the investigators are developing methods to help children grow faster. . . . As mentioned previously, immunizations and a good supplement will be provided for all children, and health education in good nutrition practice and general hygiene will be given to all mothers. . . .
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> "It might be considered as an alternative that all subjects are treated regularly with anti-helminthic drugs. However, as previously discussed there exists reasonable doubt as to whether this is of long term benefit. Also, this alternative is not a realistic possibility unless the Ministry of Health is provided with more convincing data, through a study such as this, that regular treatment is beneficial.
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> "Another alternative would be to treat only those children currently infected with *Ascaris* at the time they are seen. However, even in this trial it is not possible to examine each child's stool at the time they come to the clinic because of the large numbers involved and the difficult field conditions. (For scientific purposes, the stools will be preserved and examined in retrospect.) Because of the high re-infection rate it would be necessary to examine a stool at each visit. Also, making treatment a regular part of well-child care could only be done under conditions where no stools would be examined, and it is felt that this study should, as much as is possible, simulate real conditions of drug use.
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> "It should be noted that there are predecents for routine periodic use of anti-parasitic drugs when individuals are not examined for infection status. Such an example is the weekly administration of the anti-malarial chloroquine, which is recommended for all young children in malarious parts of Tanzania and elsewhere."

The questions posed are: in international collaborative research, 1) should American scientists insist on imposing U.S. standards of ethics in what might be considered a reverse purism in academic colonialism, or conversely, 2) could American scientists be accused of applying a double standard of ethical review if they followed local national ethical practices? This might be called "double bind" research because both accusations might be valid.

The extenuating circumstances here make the judgment easier since the practical possibilities of eventually using periodic mass ascaricidal treatment to promote improved nutrition has considerable over-riding social importance. The drug is essentially without side effects and is already widely but erratically used in this society. Regularizing the use of the drug in an epidemiologically sound clinical trial carries the potential of introducing an appropriate technology that could reduce a heavy burden on the growth of children in what has been called "this wormy world."

In clinical research where the relative risk to the individual has already been demonstrated to be minimal, commu-

***Editor's Note:** The original draft of this manuscript[1] did not address the ethical issue at any point. At the editor's request, the manuscript was modified to do so and the author(s) submitted additional background material on a proposal for a follow-up study. This material was forwarded to Dr. Taylor who refers to it in this paragraph and the ensuing quotation.

nity considerations seem dominant. Should we therefore develop a new process of community rather than individual informed consent? As justification, it can be postulated that individual decision-making is a largely U.S. obsession. Especially in Africa, health decisions are typically made by the family and community as shown in the work of several medical anthropologists, especially Janzen's beautiful study, "The Quest for Therapy in Lower Zaire."[5] Where most decisions about treatment are communal, is it only a facade to insist on individual consent? Does it not simplify and make more realistic and honest a process whereby community leaders give the consent since individuals would follow their advice in any case?

It may be that we should distinguish between situations which require individual consent and those which require community consent. The latter would be appropriate when a particular health measure has been sufficiently tested clinically to be ready for mass use in public health programs.

U.S. standards of testing have established three phases of clinical testing and this practice has spread around the world. The progression from Phase I to Phase III (general use) clinical trials follows clear Food and Drug Administration requirements based on degree of certainty about safety and effectiveness and rigor of testing. In the U.S. pharmaceutical system, after a preparation has been cleared through Phase III large scale clinical trials, it is released for general distribution through open market mechanisms.

In most countries of the world there is a trend away from uncontrolled private distribution of pharmaceuticals because it is clear that competitive market mechanisms will never provide the necessary controls to limit the excessive use of drugs. There is an unsaturatable public demand that can be pushed ever higher by clever advertising and societal hypochondria. WHO is putting great effort into promoting for each ecological area of the world appropriate local lists of essential drugs. Mechanisms will be needed to better define those drugs and health measures that society is prepared to promote rather than leaving them to float free in the market place.

In the task forces of the WHO special program for Human Reproduction Research, we identified the need for Phase IV clinical trials. When society takes on the responsibility to promote the distribution of a drug, as in national family planning programs, more information is needed than safety and effectiveness. Ethical standards need to be rethought. Acceptability and regularity of use become central. Epidemiological measurement of community impact depends primarily on coverage and the logistics of supply and distribution at the interface between the health services and the community. Focused study is especially needed on the potentials of "surveillance" and "risk" approaches in identifying by simple epidemiologic and social indices those who are in greatest need so as to ensure that they get coverage priority.

Once a new treatment is judged to have been cleared through Phase III clinical trials, there should be a new framework of testing before it is considered ready for mass distribution. Since the community is taking responsibility for promoting the program, prior standards of a positive statement of individual consent would no longer be relevant. Any individual should always have the right to withdraw from any such study. However, decisions about the initiation of a mass program should be societal not individual.

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