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Moral Maladaptation? Reflections on a Report of Research Involving the Correction of Endemic Hypothyroidism in Africa

The article by Glenn W. Geelhoed, "Metabolic maladaptation: Individual and social consequences of medical intervention in correcting endemic hypothyroidism," published in this volume of *Nutrition*, highlights the impact that seemingly simple interventions can have on a population.[1] Although the treatment of endemic hypothyroidism is simple and inexpensive, Geelhoed documents that the treatment resulted in profound and devastating effects on the population, most notably hunger and unsupported population growth. Consequently, this report might serve as an admonition to those devising public health interventions to plan carefully before instituting such measures in a population. Yet, whatever benefit this story might have with respect to future public health initiatives, the report raises a series of concerns suggesting that the study was incongruous with major ethical principles and prominent international statements intended to guide research with human subjects. Before explaining more, however, it is important to note that my analysis is derived from the information about the study provided in the manuscript and may, therefore, capture inadequately the study itself. Determining the accuracy of this analysis would likely require having the opportunity to query its author, other study personnel, and the subjects themselves, as well as to review primary study documents.

Over the past half a century, largely in response to revelations about the inappropriate use of human subjects, a series of international statements have been issued that outline procedures for ethical research with human subjects. Arguably the most important of these documents are the *Nuremberg Code* and the World Medical Association's *Declaration of Helsinki*.[2,3] Furthermore, the provisions expressed in these documents find philosophical justification in a series of well-accepted guiding principles. As articulated in the *Belmont Report*, issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, these principles are respect for persons, beneficence, and justice.[4]

Respecting persons, often referred to as the principle of autonomy, finds application in the now common practice of obtaining informed consent for participation in research. A forceful statement of this requirement is found in the *Nuremberg Code:* "The voluntary consent of the human subject is absolutely essential."[2] While obtaining meaningful informed consent can be challenging, doing so is central to respecting persons who may face substantial risk as a result of being a research subject.[5] Remarkably, there is no mention in Geelhoed's report about his informed consent procedures. Since the study described in the report would certainly seem to require consent, it is important to ask whether in fact it was obtained. If so, who gave consent? What risks, benefits, and alternatives were provided to potential subjects?

Even if informed consent was obtained and was simply not mentioned in the manuscript, the principle of beneficence requires that benefits to subjects are maximized and potential harms minimized. While endemic hypothyroidism is treatable by the methods used in the study, providing nearly certain individual medical benefit,[6] it is incumbent upon investigators to minimize risks to subjects. In this case, it seems that several of the harms experienced by the subjects were predictable. For instance, hypothyroidism is a well-recognized cause of infertility. Consequently, was the supplementation of iodine in turn supplemented with information about potential measures to control fertility? Was increased fertility as a result of supplementation understood by the subjects? Was enhanced fertility desired? Were its implications discussed? Similarly, it is no surprise that enhanced thyroid function would result in increased caloric needs. Accordingly, why weren't alternative food sources identified before supplementation? Were the subjects aware of the effects of supplementation on their caloric needs? Furthermore, would they have elected to randomly assign persons to receive treatment? Or perhaps to assign those least well off? Or would they have chosen some other strategy altogether? Regardless, the harms described by Geelhoed should have been anticipated and an appropriate infrastructure developed to deal with them.

At a broader level, beneficence requires that human subjects be used in research only when absolutely necessary. This is underscored in the *Nuremberg Code:* "The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature."[2] Given that it has long been clear that endemic hypothyroidism is treatable, should this experiment have been done in the first place? What did the investigators anticipate that they would learn that was not previously known? What was the scientific rationale for the study? If the central concern related to the effects of supplementation on the population, what would be learned by randomly assigning only some subjects to therapy? How might it have been anticipated that the study would redound into "fruitful results for the good of society"?

The report also raises some important questions about justice. In the context of research, the ethical principle of justice requires consideration of fairness at multiple points.[7] Why was this particular population selected for the study? What considerations entered into selecting the control population? Would the population that bore the risks of the experiment also benefit from its results? Was the effect of treating endemic hypothyroidism a priority from the perspective of the participants, or would other medical or social conditions take priority? To what extent was the population involved in the design of the study and the decision to proceed

with it? To meet the demands of justice, such questions require substantial consideration before embarking on a research study.

While it can at times be difficult to understand how the ethical principles for research might apply, procedural mechanisms outlined in authoritative documents can help investigators design appropriate research protocols. For instance, the *Declaration of Helsinki* mandates the following: "The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed."[3] Around the world, a variety of mechanisms, such as institutional review boards and research ethics committees, have been established to conduct prior review of proposed research involving human subjects. Such a review affords the opportunity to assess the design of a study to determine whether it has a good likelihood of providing scientifically useful information and to ensure that it adequately protects the rights and interests of the subjects of the research. In recent years, it has become commonplace for many peer-reviewed journals to require investigators to indicate whether this sort of approval was obtained.[8] While begging the question about whether prior review would have determined that the research study should not have been conducted, there is no mention in the text indicating prior review. Although prospective review can be cumbersome, investigators ought to welcome it, since it is one mechanism of protecting subjects who trust that the research in which they enroll is safe and appropriate.[9]

Having recounted several, but clearly not all, of the ways in which this report fails to assure the reader that the rights and interests of the subjects of the research were protected, it is important to ask whether it should be published. While some argue that "unethical" research should not be published,[10] others suggest that editors should use their discretion in making this decision, provided that they accompany publication with editorial commentary that raises relevant ethical questions.[11] Given the editorial decision to publish Geelhoed's report, it is important for readers to recognize the ethical questions it raises and to learn from them. While some of these questions may be an artifact of how the study was reported, there seems to be some evidence that the subjects of this experiment were not only harmed in the ways described by the author in his report, but also wronged in a moral sense. The ethical principles and international documents regarding research with human subjects are generally clear and provide various mechanisms, such as informed consent and prior review of research, to minimize the likelihood of harming and wronging research subjects. These relevant procedures must be followed in conducting research with human subjects.

As I reflect on Geelhoed's report, I am left feeling unsettled about a variety of issues in addition to the array of unanswered questions previously posed about the study. I am unsettled by the presumption that the anatomic and physiologic indices of a Western investigator were assumed to be normal in another culture. I am unsettled by the use of test procedures (e.g., HIV testing) performed as part of the study but not clearly related to the study aims, and which may have posed some risks to subjects. I am unsettled by the interpretive work in the report that suggests that an acquired trait confers an adaptive advantage when this trait itself limits fertility. And I am unsettled by the effect on the subjects themselves. What has happened to this unfortunate group of persons that briefly "tasted" a euthyroid life? How can they make sense of a short-term intervention that caused societal devastation? Who has apologized? And how can we ensure that this sort of thing does not happen again?

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