The rights and wrongs of intentional exposure research: contextualising the Guatemala STD inoculation study

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ABSTRACT

In its recent review of the US Public Health Service Sexually Transmitted Disease Inoculation Study, conducted in Guatemala from 1946 to 1948, the Presidential Commission for the Study of Bioethical Issues identified a number of egregious ethical violations, but failed to adequately address issues associated with the intentional exposure research design in particular. As a result, a common public misconception of the study was wrong because researchers purposefully infected their subjects has been left standing. In fact, human subjects have been exposed to disease pathogens for experimental purposes for centuries, and this study design remains an important scientific tool today. It shares key features with other types of widely accepted research on human subjects and can be conducted ethically, provided certain safeguards are implemented. That these safeguards were not implemented in Guatemala is what made that study wrong, rather than the fact of intentional exposure itself. To preserve public trust in the clinical research enterprise, this conclusion ought to be stated explicitly and emphasised.

Thanks to an historian’s accidental discovery, the world recently learned of yet another horrifying example of unethical research conducted on human subjects, this one hidden for over half a century. In the late 1940s, American and local researchers seeking to study prophyaxis and transmission intentionally exposed Guatemalan subjects to syphilis, gonorrhoea and chancroid by way of inoculation. Healthy individuals, patients and institutionalised children were studied by way of inoculation. Healthy individuals, patients with other afflictions, and those who had already contracted these diseases were inoculated with infectious material, as researchers sought to distinguish common STDs from one another, identify their causes and modes of transmission, understand their pathology, answer questions regarding immunity and develop cures and preventive measures. Scientific understanding of these diseases improved through the early 20th century, as did available therapies. However, substantial questions remained, leading not only to...
the Guatemala study, but also to several instances of STD inoculation research in the USA and elsewhere during and after World War II.\textsuperscript{1, 5, 6, 11}

Research in which human subjects are intentionally exposed to infection continues today—albeit under much different circumstances—as a valuable tool for proving microbial pathogenicity, defining protective antigens, identifying factors that influence disease acquisition and severity, developing vaccines, and assessing immune responses, particularly when animal models are unavailable or are of limited value.\textsuperscript{15–17} In fact, standardised approaches for this type of research have been developed for a number of diseases, including malaria, gonorrhoea and chancroid, in order to both facilitate replication of results and protect subjects.\textsuperscript{3, 15, 18}

Of course, the mere prevalence of intentional exposure research cannot do any ethical work, but recognising the existence of other examples does help to contextualise the Guatemala experiments. Particularly because many people who learn of the study express substantial surprise and concern (again anecdotally) that the subjects were infected on purpose, it seems relevant to acknowledge—and even emphasise—that this feature was relatively commonplace, and persists in research today, unlike other disconcerting aspects of the Guatemala study that have been largely resolved by modern ethical standards mandating consent, independent review, sound science, risk minimisation, special protections for vulnerable populations and the like.\textsuperscript{19–22}

**ETHICAL CONCERNS**

Given its potential for making healthy people sick, intentional exposure research certainly does warrant moral concern. However, for two primary reasons, there is a general consensus that this type of research does not warrant moratorium.\textsuperscript{19–20, 23, 24}

First, the professional roles and duties of physicians and researchers routinely diverge, with researchers focused on the creation of generalisable knowledge for the future improvement of health rather than current individual benefit.\textsuperscript{25} Thus, while physicians qua physicians are traditionally dedicated to alleviating and avoiding harm in their patients, physicians qua researchers are permitted to expose subjects to risks even without the prospect of direct benefit, without objection that they have violated their duty to give subjects’ well-being precedence over all other interests.\textsuperscript{26} Of course, we impose limits on these risks, requiring that they be both minimised and justified by the value of the information that results,\textsuperscript{19–22} but the point is that intentional exposure research does not uniquely challenge the traditional norms of medicine.\textsuperscript{15, 17, 23} In other words, physicians are expected to do no harm, but in many cases, researchers are not held to the same standard.

Second, in terms of the magnitude of harm, intentional exposure research is at least no more troublesome than certain other types of non-therapeutic research with healthy subjects. As opposed to early phase pharmaceutical studies that involve a great deal of uncertainty with regard to both the nature of potential risks and their severity and permanence, intentional exposure research can be designed in such a way that the risks are well-defined in advance and subjects can be reasonably assured that they will walk away as healthy as they were at the outset. On the other hand, assuming infection is successful, they can usually expect some level of discomfort, but this is similarly true for phase I trials in which subjects are used to determine the maximum tolerated dose of investigational products, for example.\textsuperscript{17, 23}

Potentially harmful non-therapeutic research is not without controversy, but it is nonetheless permitted as integral to the progress of medicine. Unless we are prepared to give up phase I research, which can impose even greater risks and harms on subjects, there is no consistent reason to oppose intentional exposure research; exposure to toxicity versus infection is not itself a morally relevant difference.

**CURRENT ETHICAL STANDARDS**

Upon closer examination, intentional exposure research is not as disconcerting as it may initially appear. However, in addition to standards applicable to all clinical research involving human subjects,\textsuperscript{19–22} modern frameworks suggest a number of specific safeguards to clarify what it means for risks to be minimised and reasonable in this context.\textsuperscript{16, 17, 24} First, there must be a strong rationale for selecting the intentional exposure design. Alternatives need not be absent if this approach would be substantially more efficient at generating important data since these efficiency benefits may outweigh the risks, but human exposure research should not proceed when animal research could yield the same knowledge, and it should involve exposure of as few subjects as possible. The disease under study should be well-characterised and either self-limiting or fully treatable, while subjects should be carefully selected and monitored to prevent serious or irreversible harm. The duration of subject illness should be as short as possible, and discomfort during the study should not be excessive. Individuals beyond the study should be protected from infection through isolation of subjects as appropriate and limiting the duration of infectivity, but the protections selected should be the least restrictive of subjects’ freedom. Finally, subjects should be capable of understanding the risks and willing to volunteer on their own, meaning that intentional exposure research should not be conducted with groups of subjects who may be particularly vulnerable, such as children, incompetent adults or prisoners.\textsuperscript{16, 17, 24} Importantly, many of these safeguards apply with equal force to other types of risky non-therapeutic research.

**CONCLUSION**

What happened in Guatemala is both shocking and disturbing, but what went wrong was precisely what the President’s Commission identified: involuntary participation, unacceptable risks and sloppy science—not intentional exposure itself. Considering how unsettling intentional exposure research might appear at first glance, this more nuanced conclusion ought to be stated explicitly and should be underscored.\textsuperscript{23} Thus, when the public asks whether the Guatemala study could happen today, the appropriate response is twofold: modern standards and practices render repetition of its particular amalgam of ethical violations highly unlikely,\textsuperscript{1} but intentional exposure research continues as an important scientific tool for improving human health. It can be done right.

**Contributors**

HFL is the sole contributor to this brief report.

**Competing interests**

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**REFERENCES**
