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EDITORIAL

Human Experimentation: Historical Lessons

Medical research directed towards the development of new therapeutics and vaccines is a long drawn out complex affair, in which the chances of success are relatively slim. The regulatory process, that seeks to ensure the safety of vaccines and drugs intended for human use, involves different phases of clinical trials, which require the participation of volunteers. 'Informed consent' is a stated necessity, implying that all participants in a clinical trial are fully aware of the risks that they may be exposed to in the course of the study. Major pharmaceutical companies are increasingly fanning out to developing or underdeveloped countries to conduct clinical trials, most often drawing participants from poverty stricken populations, with limited understanding of the risks that may be involved. In attempting to secure the hundreds of millions of dollars invested in research on new therapeutics or vaccines, there is a strong desire to push ahead with clinical trials. The mushrooming of 'clinical research organizations' in India, sometimes a euphemism for entities that undertake and facilitate clinical trials on a contractual basis, is a clear indication that major multinational pharmaceutical companies are indeed eyeing India's large population as a fertile prospect for testing new products. Several recent controversies raise concerns about the manner in which trials have been planned and conducted. While reports in the press highlight and sometimes sensationalize ethical lapses, there is a clear sense of unease in the many commentaries on clinical trials that have appeared over the last year. Medical research involving human subjects has always been an ethical minefield. Indeed, much of the internationally accepted guidelines emerged after the Nuremberg trials, which convicted as war criminals German doctors who carried out the most brutal experiments on prisoners in the name of medical research. The Nuremberg Code (1947) provides today a starting point for considering experiments involving humans.

Discussions of ethics in human experimentation need to be informed by the lessons of history. A recent editorial in *Nature* entitled 'Hypocritical oaths' comes to the conclusion that 'history judges some research as unethical, despite approval at the time' (*Nature*, 2012, **482**, 132). Indeed, hindsight can be a powerful weapon of judgement on most human matters. The *Nature* editorial quotes William Osler's prescription that appeared over a century ago: 'For man absolute safety and full consent are the conditions which make such tests allowable.' The provocation for *Nature*'s editorial concern is a news fea-

ture on human experiments carried out by US doctors in Guatemala beginning in the 1940s. The article attracts immediate attention with the headline, 'First, Do Harm' (Walter, M., *Nature*, 2012, **482**, 148). The Guatemala venereal disease experiments were exposed only in 2010, when Susan Reverby, a historian, published an account of a horrific series of studies carried out with human subjects, with the 'full knowledge of US health officials' in the late 1940s (*J. Policy History*, 2011, **23**, 6–28). Her discovery of the Guatemala papers in 2009 was accidental. Reverby had just completed her book *Examining Tuskegee: The Infamous Syphilis Study and its Legacy* (University of North Carolina Press, Chapel Hill, 2009). One of the researchers in the Tuskegee study John Cutler had left his papers at the University of Pittsburgh. In searching for additional material on Tuskegee, Reverby chanced upon details of Cutler's experiments in Guatemala. The Guatemala studies began in 1946 when penicillin had become available as an effective treatment for syphilis. Yet in these experiments uninformed subjects were deliberately infected and treatment withheld (Semenuk, I., *Nature*, 2010, **467**, 2010). The extraordinary cruelty of the experiments and the decades long suffering of the subjects is described in the news feature in the 9 February 2012 issue of *Nature*. The author provides a historical rationale for what appears in retrospect, as an abhorrent study: 'In the early decades of the twentieth century, US health officials were consumed by the battle against sexually transmitted diseases, much as subsequent generations of researchers have fought cancer and HIV.' In 1943 an estimate was made that the US army would be challenged by '350,000 new infections of gonorrhea annually'. This in turn was termed as 'the equivalent of putting out of action for a full year the entire strength of two full armored divisions or of ten aircraft carriers'. The end of the war in 1945 and the availability of penicillin by then suggest that the Guatemala experiments were ill-conceived and appear to have been devised and approved by researchers and administrators 'who cut their teeth with venereal diseases and were interested in them'. The studies conducted by Cutler in Guatemala had the support of local public health officials and the political leadership. Indeed over six decades later local governments in poor countries often facilitate 'clinical trials' carried out with little oversight by pharmaceutical companies and international agencies. In the aftermath of Reverby's account of Cutler's experiments, a US bioethics commission

produced the grim statistics, over sixty years later. 'Cutler's team exposed 558 soldiers, 486 patients at the psychiatric hospital, 219 prisoners, 6 prostitutes and 39 other people to gonorrhoea, syphilis or chancroid. But the commission was unable to determine how many people actually developed infections or how many of the participants were treated. Researchers also measured the accuracy of diagnostic tests in experiments that involved orphans and people with leprosy, as well as people from the psychiatric hospital, prison and the army.' Some descriptions of Cutler's experiments, described in the *Nature* news feature are reminiscent of the bizarre and brutal details that emerged at Nuremberg. Even in retrospect it appears difficult to provide a historical rationale for the Guatemala study.

The lead researcher in this bizarre episode, John Cutler, began his career in another controversial project initiated by the US Public Service in 1942. Driven by the desire of the military to develop prophylactic methods against sexually transmitted diseases, Cutler participated in an experimental program using 'volunteers' at a prison in Terre Haute, Indiana. The *Nature* news feature notes that this short-lived study which lasted only ten months 'established several practices that Cutler would go on to use in Guatemala'. The experiments in Guatemala between 1945 and 1948 have been termed 'not only an unconscionable violation of ethics' but 'also poorly conceived and executed'. Curiously, failure and poor practice did little to retard the progression of Cutler's career. Interestingly 'the World Health Organization sent Cutler to India to lead a team demonstrating how to diagnose and treat venereal disease'. A decade or more after his Guatemala experiments, Cutler arrived in Alabama, then a racist bastion, to become 'a lead researcher in the infamous Tuskegee experiment...in which hundreds of black men with syphilis were studied for decades without receiving treatment'. The *Nature* feature notes that 'he flourished in the Public Health Service and later became professor of international health at the University of Pittsburgh'. The Guatemala papers were unearthed several years after his death in 2003. There will undoubtedly be many analyses in future which will attempt to understand the man and his actions in the context of the times he lived in and the environments in which he worked.

Tuskegee, where Cutler found another location for his experiments in the 1960s, is now synonymous with unacceptable protocols in human experimentation. The website of the Centers for Disease Control and Prevention provides a timeline for the 'Tuskegee Study of Untreated Syphilis in the Negro Male'. The experiment, which began in 1932, involved as many as '600 black men - 399 with syphilis, 201 who did not have the disease'. The subjects did not know that they were part of an experiment designed to 'record the natural history of syphilis'. The ostensible purpose was to study disease progression in untreated patients. The study ran for forty long years until a news report in 1972 led to termination of the experiment. Although penicillin became available and was the preferred treatment by the early 1950s, 'the men

did not receive therapy'. A scholarly account of the Tuskegee experiment entitled 'Racism and research: The case of the Tuskegee syphilis study' appeared in 1978 (Brandt, A. M., *The Hastings Center*, December 1978, pp. 21-29). The investigations that followed the public disclosure of the details of the experiment did not, in Brandt's words, address 'the most basic questions of *how* the study was undertaken in the first place and *why* it continued for forty years'. Brandt goes on to suggest that the origins of the Tuskegee experiments were rooted in the then prevailing medical opinion that viewed black Americans as 'essentially primitive peoples', in the early years of the 20th century. 'By the turn of the century Darwinism had provided a new rationale for American racism... Social Darwinists analyzed census data to predict the virtual extinction of the Negro in the twentieth century.' A major assumption that provides a 'backdrop for examining the Tuskegee Syphilis Study' is that doctors 'generally discounted socioeconomic explanations of the state of black health, arguing that better medical care could not alter the evolutionary scheme'. Brandt cites a great deal of correspondence in the run up to the Tuskegee study, which provides a disturbing insight into the attitudes of the men who planned the study. Why did the Tuskegee study continue for so long?; throughout the decade of the 1960s even after the many discussions of ethics in research that followed the Nuremberg trials. As late as 1969 physicians at the Center for Disease Control met, deliberated and endorsed continuation of an experiment that denied treatment to subjects infected with completely susceptible organisms. It is quite likely that the study may have continued for the lifetime of the subjects, if a press report had not drawn attention to a programme designed in a manner clearly violative of all accepted canons of medical ethics.

Brandt's conclusion is disturbing: 'In retrospect the Tuskegee study revealed more about the pathology of racism than it did about the pathology of syphilis; more about the nature of scientific inquiry than the nature of the disease process.' He goes on to add that 'the notion that science is a value free discipline must be rejected'. A final note of caution, that is particularly relevant even today, argues that 'the need for greater vigilance in assessing the specific ways in which social values and attitudes affect professional behaviour is clearly indicated'. The Guatemala and Tuskegee studies were clearly unethical, even by the standards of the times. In the former, subjects were brutally infected and, at times, left untreated. In the latter, proven treatments were deliberately withheld, for a scientific purpose which must have appeared completely unacceptable even at the time the study was conceived. Human arrogance prevailed in both cases. Presidential apologies eventually appeared; Clinton in 1997 for Tuskegee and Obama in 2010 for Guatemala. In today's context the urge to breach ethical boundaries can be strongly fuelled by commercial interest. Learning from history may be prudent.

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