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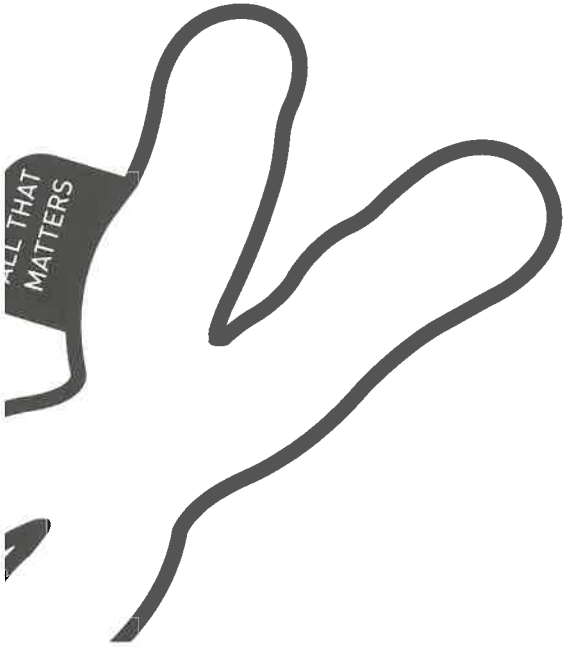
Sacrificial lambs and professional guinea pigs: a bestiary of research ethics



It's 1946. In the dock on one side of the Atlantic, Nazi doctors are being tried at Nuremberg by US prosecutors for crimes against humanity, in the form of 'research experiments' carried out on concentration camp prisoners. And on the other side in Guatemala, the US Public Health Service (PHS) is deliberately infecting prisoners and mental patients with syphilis in another 'research experiment', with the goal of creating a prophylactic against the disease to replace the ineffective drugs used for soldiers during the war that just ended.

Sixty-three years later, an American historian, Professor Susan Reverby, was rummaging through archived medical papers from the 1940s. Reverby was completing a final task in her two decades of studying the PHS's detestable Tuskegee experiments – in which hundreds of African-American men with late-stage syphilis were observed but not treated, even after penicillin was developed. She was examining the papers of Thomas Parran, US surgeon-general from 1936 to 1948, when the Tuskegee research was already in full swing.

And so, she found, was the previously unknown Guatemalan 'experiment'. For years Tuskegee has been a byword for abuse of research ethics – to the extent that President Clinton apologized to its surviving 'subjects'. But Reverby was to find that, if such a thing were possible, Guatemala was an even more egregious abuse. As she said,

> *Flashing red lights. I'd spent nearly two decades explaining that there had been no inoculation at Tuskegee, that while the PHS had used deplorable*

ethics, they had never infected anyone with syphilis. And here it was . . . the US government's health service had deliberately infected 427 Guatemalan men and women, prisoners and mental patients, with syphilis.[1]

The US prosecutors at Nuremberg didn't know about the Guatemala experiments at the time of the Nuremberg trials, so there's no allegation of deliberate hypocrisy. That's not the issue. Instead, the questions are:

- How were the public health authorities able to override the basic medical ethics rule of 'First do no harm'?
- Why didn't they think informed consent was necessary?
- How was a rich developed country able to persuade a weaker, poorer country to sacrifice its nationals – particularly when that involved very vulnerable populations, prisoners and mental patients, who have also been used as trial subjects in a number of other abuses of research ethics?[2]

Guatemala and Tuskegee were extreme examples of abysmal research ethics, and they happened many years ago (although the Tuskegee 'experiment' went on until 1972).[3] As the US bioethicist Art Caplan has said about the Guatemala case:

> *When you give somebody a disease – even by the standards of their time – you really cross the key ethical norm of the profession.*[4]

You might think that such an outrage couldn't happen any more. Bioethicists disagree among themselves about that, with Dan Brock at Harvard Medical School calling it 'pretty unlikely' but Eric Meslin at the University of Indiana warning that 'it could happen today'.[5] After President Obama, like his predecessor, issued an apology, he appointed a presidential bioethics commission to look at the adequacy of standards – which indicates that the president agreed with Meslin rather than Brock.

Tuskegee and Guatemala were examples of bad science as well as bad ethics, so it's not entirely fair to use them as examples of what untrammelled 'scientific curiosity' can lead to. But the issues about whether and how research ethics should be deployed to prevent science doing whatever it can do – that theme from Chapter 1 – keep on recurring, albeit in guises that make them harder to spot than blatant wrongs such as the Nazi atrocities, the Tuskegee case or the Guatemalan study. More typically, they now concern economic exploitation or cultural clashes rather than medical risk – although that element certainly hasn't disappeared, especially when poor and vulnerable subjects are tempted to accept risks for reward.

The Nuremberg Code

The Nuremberg trials resulted in the Nuremberg Code, which was supposed to prevent Nazi-style abuses from recurring by settling issues like informed consent and doing no harm, even though the code was voluntary. Its successor, the Declaration of Helsinki, has gone through several revisions but is still the agreed standard today. The fact that there are agreed standards puts research ethics ahead of other controversies

in bioethics – such as genetic patenting, where the issues are still being dragged through the courts. Below is the crucial first paragraph of the Nuremberg Code:[6]

> *The voluntary consent of the human subject is absolutely essential. This means that the person involved should have the legal capacity to give consent, should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud . . . or other form of constraint or coercion; and should have sufficient knowledge and comprehension of the subject . . . to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected and the effects on health which may possibly come from his participation in the experiment.*
>
> *The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment.*

Ironically, the Tuskegee and Guatemala experiments have actually been explained in terms of national solidarity. Along with studies such as the 1942 trial in which Michigan mental patients were deliberately exposed to flu after being injected with an experimental vaccine – a trial in which a younger Jonas Salk was co-investigator – they were ostensibly justified in terms of the urgency of conquering killer contagious diseases and benefiting the nation as a whole. In the words of Laura Stark, a US professor of science in society:

> *It was unusually unethical, even at the time . . . [But] there was definitely a sense – that we don't have today – that sacrifice for the nation was important.*[7]

We heard something similar at the time of Hwang Woo Suk's experiments, during the euphoria before the truth was revealed: that Korean women were willing, cheerful and patriotic sacrificial lambs. That's all very noble, but whose sacrifice is expected for whom? Why should poor African-American men have been expected to sacrifice their health, without even a by-your-leave – and for no predictable benefit? And why should Guatemalans make sacrifices for another nation altogether?

That contradiction is all the more acute now that a substantial proportion of clinical trials are 'outsourced' to the Third World – a phenomenon that outstrips 'reproductive tourism' and 'surrogacy contracting' to India, although the same dynamic is at work. A report in 2010 revealed that foreign citizens made up more than three-quarters of all the subjects in clinical trials conducted by US firms and researchers. The US Food and Drug Administration inspected only 45 of these sites, about 0.7 per cent. This isn't altogether a new phenomenon: it's been alleged that the PHS had deliberately moved the Guatemalan study abroad from Terre Haute, Indiana, because offshore testing wasn't subject to the same level of scrutiny.[8] The director of the Guatemalan research may have believed he

was doing good science, but he also wrote to his own supervisor:

> *Well, all I can say is, it's against the law to do many things, but the law winks when a reputable man wants to do a scientific experiment . . . Unless the law winks occasionally, you have no progress in medicine.*[9]

There's no suggestion that Third World patients are deliberately being made ill when research is outsourced there these days – unlike in the Guatemalan case – but there have been controversies about whether populations lacking basic medical care are inherently vulnerable. Can they really make an informed choice about whether to enter a clinical trial when the choice may be either participating in the trial or receiving no medical treatment at all? The Nuremberg principles weren't and couldn't have been devised to deal with this sort of situation: the absence of genuine consent from the concentration camp prisoners was obviously of a different sort altogether.

During a major meningitis epidemic in 1996 in northern Nigeria, the drug company Pfizer supplied doctors with the oral antibiotic Trovan®, which the firm wanted to test against the most effective known drug, ceftriaxone, as a 'control'. This procedure is actually consistent with the Declaration of Helsinki and with the general consensus in research ethics that the control group has to receive the best known treatment for comparison.

The Trovan trial was arguably less controversial than an earlier case, in which pregnant African women with human immunodeficiency virus (HIV) were enrolled in trials about preventing transmission to their fetuses. There, researchers were comparing a low-dosage anti-retroviral regime not with the best known treatment available in the West, but with a placebo – on the grounds that what was relevant was the best locally available treatment (nothing).

Even that trial provoked opposite reactions: proponents, including many African commentators, favoured the trial because if the cheaper low-dosage regime succeeded, it would be more likely to be taken up in Africa than the expensive 'gold standard' treatment.[10] But shouldn't the standards of care in clinical trials be universal, not dependent on the colour of the subjects' skin?

Yet the Trovan trial also stirred up a storm, for two different reasons. First, even if the trials were favourable, Trovan was never intended for sale in Africa, but rather in the USA and Europe. Second, the sparse clinical teams were already facing not one but three epidemics – measles and cholera as well – so both they and the children's families were desperate. In the words of Jean-Hervé Bradol, who was president of Médecins sans Frontières and in charge of the African teams:

> *It was not a time for a drug trial at all. They were panicking in the hospital, overrun by cases on the verge of dying. The team were shocked that Pfizer continued the so-called scientific work in the middle of hell.*[11]

Eleven children died during the Trovan trial, while others were permanently disabled; several families have brought a complaint, and Pfizer has settled with the Nigerian government (without admitting responsibility).

However, the death rate during the Trovan trial was well below the rate for untreated meningitis – and was much the same in both arms. Five children died on Trovan, six on the control drug (ceftriaxone).

So you could certainly argue that the children who were saved by the Trovan trial benefited, even if in future other African children stricken with meningitis weren't going to be offered the drug. And perhaps you could also speculate that the success of the trial, in those terms, made it more likely that there would be pressure on the drug company to lower its prices and make Trovan more widely available. That did happen with anti-retroviral drugs for HIV in South Africa.

But is that good enough? When trials are outsourced abroad, or delegated to private profit-making companies, how can the Nuremberg or Helsinki principles be monitored? In principle, regulation is supposed to be up to Institutional Review Boards (IRBs) at the principal investigators' host institutions (local research ethics committees in the UK) or to the grant-giving bodies behind them. Researchers often complain that regulation is, if anything, too constricting, stifling medical research and investment. In the words of a recent report from the UK's Academy of Medical Sciences:[12]

> *[T]here is evidence that UK health research activities are being seriously undermined by an overly complex regulatory and governance environment . . . [A]fter funding for a study has been agreed, it now takes an average of 621 days to recruit the first patient. In short, the current situation is stifling research and driving medical science overseas.*

This is a common complaint on both sides of the Atlantic, but not one that impresses the US bioethicist Carl Elliott. In his neatly titled book *White Coat, Black Hat: Adventures on the Dark Side of Medicine*, Elliott has explored the unregulated netherworld of professional guinea pigs. Like the African subjects of the Trovan trials, these Americans aren't going to reap any benefits from the drugs they test for a living, because they're poor and uninsured. That's why they're the only ones willing to become guinea pigs for phase I trials, which are designed to test toxicity.[13] But if those trials go wrong for them, only 16 per cent of US academic medical centres will cover their healthcare.[14]

Many IRBs, Elliott charges, are themselves also for-profit concerns, sometimes funded by the very companies they're meant to regulate. In one case, a 'sting' operation conducted by the General Accountability Office and a congressional committee discovered that a Colorado IRB was happy to approve a 'clinical trial' for a non-existent company wanting to test a fraudulent, unproven medical product.[15] In fact, over 70 per cent of US drug trials in 2004 were conducted in the regulation-lighter private sector.[16]

The dominance of private financial interests in publicly funded or targeted research is one thing that's changed since the Nuremberg Code. Another is the way in which informed consent is no longer just a matter of not experimenting on unwilling individuals. You'd think that might be simple, but it's not, particularly where cultures collide. We saw an example of that in the Tongan case in Chapter 4.

A more recent controversy has involved a biobank – a collection of stored tissue samples – taken from the Havasupai tribe in northern Arizona, who filed a $50 million lawsuit claiming that Arizona State University (ASU) researchers had improperly used their members' blood samples. They alleged lack of properly informed consent – along with fraud, breach of fiduciary duty, negligence and trespass.

Twenty years earlier, ASU scientists had collected over 200 blood samples from tribal members, in what the tribal elders had been told was a study of diabetes. The consent form was broader – too broad, in fact, with its vague wording about studying 'the causes of behavioral/medical disorders'. And true to the waffly wording of the consent form, the researchers used the samples for multiple studies unrelated to the research on diabetes – which hadn't panned out – without informing the Havasupai.

Tribal members later discovered – and objected to – use of the samples in studies on schizophrenia and inbreeding. They claimed that the resulting two dozen published scientific papers had damaged and stigmatized the tribe.[17] While this objection was widely reported in the press as having to do with Havasupai cultural beliefs, anyone might be nervous about being stigmatized as schizophrenic or inbred in published articles with the apparent authority of science behind them. But the Havasupai did also object to evolutionary genetics studies performed on the samples, throwing the tribe's origin stories into doubt.

The Havasupai couldn't really have expected to win: a number of precedents were against them. Other groups or individuals have also challenged 'blanket' consents to use of their tissue or data in biobanks for other purposes than they intended, and they've generally lost.[18] Nor, as we saw earlier, does the common law recognize that you can have property rights in tissue once it's left your body.

But the university did (eventually) apologize, settle out of court for $700,000 and agree to return the remaining samples to the tribe. This sets a possible legal precedent (although there was no court judgment) and does raise difficulties for researchers about whether they need to obtain a fresh informed consent for every new use of stored samples. But then the question is whether the initial 'consent' was really 'informed'.

Researchers might be forgiven for thinking that the principles of research ethics only require them to be open and honest about medical risks. That's what the Nuremberg Code is concerned with:

> *'Informed consent' requires that before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected and the effects on health which may possibly come from his participation in the experiment.*

That's actually quite a lot to do, without worrying about social or cultural risks such as stigmatization. On the

other hand, the intent of the Nuremberg Code is clearly to make researchers be as open and specific as possible with their subjects – and a vague blanket consent form ('the causes of behavioral/medical disorders') certainly goes against that grain.

The dilemmas of biomedical research haven't lessened since Nuremberg: like pluripotent stem cells, they've just changed shape. What has changed is the public climate in which research takes place. Jean McHale, a British professor of medical law, thinks our attitudes have swung round 180 degrees since Nuremberg: now, she says, we assume research is never wrong.[19] The claim that we have a positive duty to participate in medical research demonstrates exactly that attitude.

You could almost say we have a quasi-religious attitude to medical research. And that leads us nicely into the concerns of the final chapter: 'God, Mammon and biotechnology.'

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God, Mammon and biotechnology

The notion that science and religion are at war is one of the great dogmas of the present age.[1]