# 5

# Grounds for Comparison

## Biology and Human Experiments

A belief in the universality of biology does not make all bodies the same; rather, it establishes a set of agreed-upon rules about how the human body is assumed to work, and it establishes hypothetical equivalences between them. Human biology becomes, then, what we call a 'standard', a yardstick that can be used to measure difference in terms of variation from a norm, and in this way bodies are made commensurable. The previous chapter explored how biological standards were used for intervening in epidemics, maternity and famines, spawning a global biomedical enterprise that was borne, initially, on the tide of colonial efforts to improve health in distant lands and, subsequently, by means of humanitarian campaigns. Use of a biological standard makes possible structured and rigorous comparisons of bodies, both human and non-human, a practice that has become the cornerstone of biomedical knowledge. The apotheosis of biological equivalence and the comparative, scientific enterprise is experimental medicine, epitomized in the randomized clinical trial.

In this chapter, we examine how scientific biomedicine emerged from practices of comparison made possible by assumptions of biological equivalence. Anthropologists are increasingly involved in biomedical research, particularly as clinical trials have become both globalized and are, quite often, greeted with suspicion and even outright resistance. This growing body of ethnographic evidence reveals unintended consequences and troubling implications associated with this experimental enterprise. We focus specifically on how clinical trials have been contested at local sites, and show how they are deeply embedded in social relations that undermine epistemological claims of 'objectivity'. Furthermore, such trials are woefully ill equipped to recognize, much less address, glaring political and social inequalities in the incidence of disease and illness in any given population because biologically standardized groups are enrolled as subjects, and attention is narrowly focused on outcomes within the duration of the clinical trial alone, thereby bracketing out how social inequalities both produce and modify biological responses to biomedical interventions.

## The Laboratory as the Site of Comparison

The rise of the 'experiment' in biomedicine is associated with the objectification of nature, and hence of the body, that emerged gradually after the Enlightenment. Internal pathology began to be made visible when autopsies became routine, and by the nineteenth century a systematic approach to the investigation and naming of diseases based on autopsy findings was in place. This approach, a nosology of disease, was complemented by use of quantitative methods to study the distribution of illness in the clinic that, as we will see, was increasingly applied to entire populations beyond the clinic.

*An Anthropology of Biomedicine*, Second Edition. Margaret Lock and Vinh-Kim Nguyen.

Claude Bernard's *Introduction to Experimental Medicine*, published in 1865, is recognized as having made a major contribution to initiating the era of modern experimental medicine. An assumption that much can be learnt about the structure and function of human bodies from research using animals has a very long history but Bernard went further, and argued for the application of scientific methods to the understanding of disease by carrying out experiments on animals in the laboratory. These experiments were designed to discern the chemical processes that maintain health in all living bodies, and to establish that animals could serve as 'models' of human physiological processes. For Bernard, the basis of science, and the experiment, was the method of comparison between what one might expect to see and what one actually sees as a result of experimentation.[1] Prior to the introduction of animal models, comparison could usually only take place in the mind of the physician on the basis of his experience, although at times direct comparison became possible in the clinic between patients with very similar symptoms. In the laboratory, however, controlled manipulation of animals offered the possibility of deliberately creating the circumstances in which comparisons might be made. Laboratory research began with systematic, replicable investigations into physiological mechanisms, cellular pathology and bacterial action, largely conducted on animals, and designed above all to obtain 'proof' of a mechanism or of therapeutic efficacy. When Louis Pasteur famously inoculated cows with cowpox and sheep with anthrax to demonstrate the effectiveness of his vaccine, he showed that the laboratory need not be hidden away in a hospital or university, and that powerful comparisons could be made in the real world for all to see.[2]

Despite its initial successes, experimental medicine was fraught with problems. The applicability of animal models to humans was contested, particularly in light of interspecies variation. Research on *Vibrio cholerae* is a classic example of the difficulties encountered, because simply introducing the germ into animals failed to produce cholera-like symptoms, which raised questions about the worth of a model that also required animals to be extensively and viciously manipulated.[3] Nonetheless, by the early years of the twentieth century, the laboratory was playing an increasingly important role in elucidating disease processes and developing effective treatments. It was not until World War II that therapeutics were systematically being developed and tested in the laboratory.[4] The sites of laboratory research had also begun to expand from their origins in the European heartland and the chemical factories along the Rhine to the outermost reaches of European empires, where field laboratories used to study exotic tropical diseases that afflicted settlers developed into networks of research institutes dotted throughout Africa, Asia and Latin America.

## The Colonial Laboratory[5]

Although in the mid-nineteenth century Pasteur provided powerful evidence of the microbial origin of disease with his famous anthrax experiment, Pastorian theories and biomedical practices, notably vaccination, were initially met with resistance by medical doctors and the public health establishment in France. Only after World War I did the French establishment become convinced of Pasteur's findings, as has been detailed by the historian and sociologist of science Bruno Latour in his aptly named book *The Pasteurization of France*.[6] Latour shows how the germ theory of disease slowly gained traction in France, effectively granting microorganisms the power to reshape society. Older ideas of miasma were displaced by germ theory, transforming practices of sanitation and hygiene as well as government policy. Germ theory even brought about changes in how the relationship between nature and society was viewed and acted upon[7] – in the colonies, Pastorian ideas drew attention away from climate and geography, where it had been directed by miasma theory, to focus instead on indigenous populations now



thought of as 'reservoirs' of disease. In colonial societies, these 'native hosts' of disease were unable to resist endemic disease eradication campaigns informed by the novel Pastorian ideas. The political context of colonialism thus afforded ever-greater traction for germ theory, making germs de facto actors in society, alongside humans.[8]

With military precision, Pastorian campaigns in Africa were led by colonial physicians who mapped and segmented colonial territory thus producing a sophisticated and centralized apparatus that methodically applied testing and treatment to the populations residing within. Successful campaigns to eradicate infectious diseases led by Pastorians, such as those by Jamot discussed in the previous chapter, did not go unnoticed. Indeed, they set the stage for later 'vertical' disease eradication approaches targeting individual diseases, such as those that (successfully) eliminated smallpox in the 1970s and (less successfully) targeted polio in the 1990s.

The global network of Instituts Pasteur tested and consolidated Pastorian theory (today called microbiology) and trained generations of key colonial officials.[9] These Instituts became the vanguard of tropical disease research, initially financed largely by philanthropy. Along with the Instituts Pasteur in French Indochina, Tunisia, and Senegal, the Rockefeller Institute in New York, the Wellcome Trust in London and the Fundación Oswaldo Cruz in Brazil established research laboratories that together girdled the earth. In the European capitals, training institutes such as the London School of Hygiene and Tropical Medicine, the Antwerp Institute for Tropical Medicine, and the Royal Tropical Medicine Institute in the Netherlands produced the next generation of global researchers. Their findings demonstrated the microbial origins of many diseases found around the world, thus demonstrating that biological explanations appeared to hold across different environments and cultures. This was the first step towards a global epidemiology that would later become established in association with international institutions that began to collect and compare health statistics across nations during the interwar period.[10] These institutions laid the groundwork for the foundation of the World Health Organization.[11]

Latour refers to Pasteur's pedagogy as a 'theatre of proof'.[12] As discussed in the previous chapter, while the medicalization of fertility and nutrition showed the generalizability of biological approaches to human vitality, it was germ theory that most convincingly demonstrated the biological commensurability of humans, making the colonies the theatre of proof for microbiology. The Pastorian shift towards a microbial theory of disease causation structured a powerful imaginary of the colonies as vast laboratories where the enactment of hygienic measures could be tested and the results compared across time and space. On the colonial stage, proofs of efficacy that gradually accumulated confirmed the underlying doctrine of biological commensurability, allowing lessons learnt there to be repatriated to Europe as tried-and-true practice, rather than simply as theory. The extrapolation of lessons from colonial sites was not confined to questions of health; many techniques of modern government – urban planning, fingerprinting, issuing identity documents, and so on, were first tried out in the colonies before being implemented in imperial homelands.[13] The majority of these practices sought to manage space and people in terms of 'hosts', 'reservoirs', and 'infectious pathogens', all key concepts in microbiology. In other words, the social and political conditions in the colonies, where colonial powers were not constrained in the implementation of new policies, made them a testing ground from which proven policies could be repatriated.

Population health practices in the colonies were not, however, grounded in the kind of statistical comparisons used today. Statistics, a technology of the state, began as a formal practice for counting and sorting populations by European governments in the nineteenth century. Such quantification was not systematically applied to the colonies until well into the twentieth century. In the absence of a quantifying, modern state apparatus, with its tentacles of power distributed throughout the nation, colonial administrators had but a patchy view of the populations

they subjugated, who could only be systematically counted by rounding them up by force. The numerical demonstration of biomedical efficacy was therefore confined to military forces in the colonies and, increasingly, to those populations who could be enrolled into an experimental apparatus and thus counted, a practice that is expanding exponentially today.

## Experimental Bodies

Infamous examples have tainted experimental medicine in the popular imagination. In the United States, the notorious Tuskegee Study of Untreated Syphilis in the Negro Male was conducted on African American men in the town of Tuskegee, Alabama. Carried out over 40 years between 1932 and 1972 by the US Public Health Service, poor African American men with syphilis – 399 in all – were recruited and observed in order to characterize the 'natural history' of syphilis: that is, to describe the course of the disease without treatment. Even when effective therapy with penicillin became available, the study subjects were not treated; 28 died of syphilis, another hundred died from complications due to the infection, and 40 wives and 19 children were infected. The history of this experiment has been the subject of several books and many scholarly papers and is often cited as the reason why to this day many African Americans are suspicious of clinical trials and indeed of biomedicine in general.[14] The condemnation of experiments conducted in Nazi Germany, such as those by Dr Josef Mengele, resulted in the formulation of the Nuremberg code of research ethics in 1947, although this code came too late to affect the treatment of the Tuskegee men. Japan also conducted human experiments during its occupation of China in World War II, and less controversial experiments were conducted across the colonial world, largely to find treatments for tropical diseases.

'Experimental bodies', notes the medical historian Ilana Löwy, 'are entities which can be substituted for patients' bodies in order to investigate diseases and look for treatments.'[15] Colonial and, more infamously, Nazi and Japanese experiments point to how political circumstances contribute to the production of experimental bodies, most often the bodies of marginalized, stigmatized, or oppressed populations who 'stand in' for the bodies of everyone else. Confinement and other forms of social control contributed to making these bodies easily available to medical researchers, and their scientific interest points to the waning of racist ideas of biological difference. At the time, these circumstances were assumed to be of no relevance to the knowledge generated. It was not until much later that data from these experiments was viewed as ethically tainted and therefore off limits.

As Löwy points out, most of the work on experimental bodies takes place in laboratories, with the notable exception of clinical trials that make use of large, statistically valid samples of research populations. Live laboratory animals; their organs and tissues; human tissues, cells, and genetic material; and human subjects all fall under the rubric of experimental bodies used to facilitate quantification, comparison and replication of results. Löwy notes the way in which experimental bodies are 'easier to control' than real-life bodies, creating remarkably homogenous laboratory entities ranging from genetically modified animals to tumours suitable for experimentation.[16] By the 1950s, it had become possible to genetically manipulate laboratory animals on a large scale, allowing animals to be designed according to researchers' specifications, and more recently to engineer human genes into animal bodies, in effect standardizing experimental animals. Karen Rader has written the history of the genetic standardization of the laboratory mouse, the most famous example being the OncoMouse®, patented in the United States after a long legal struggle.[17]

While it is possible to biologically standardize the bodies of laboratory animals through breeding and, later, direct genetic manipulation, this, of course, could not be the case with



humans. Generating scientifically credible knowledge about human bodies required another approach, one that had to grapple with the ethical impossibility of manipulating human bodies to make them the same. A central dilemma of comparison in biomedical experiments is that bodies are assumed to be biologically equivalent, but even today biomedical experiments are more likely to be conducted on the bodies of the economically disadvantaged whose bodies as a result differ from those who have been born into and matured in affluent environments. Anthropologist Robert Abadie studied 'professional guinea pigs' in a large American city,[18] and found that many participants enrolled in clinical trials in order to earn money because the 'compensation' offered participants was more than they would earn in the low-paying jobs they would otherwise occupy. The attractiveness of the 'job' clinical trial participant meant they often hid details about their lifestyle (such as diet or even consumption of drugs) that could influence the clinical research.

## Rise of the Clinical Trial

'Natural experiments' refer to spontaneously occurring variations in circumstances that can be observed in order to deduce their potential effect(s). The administration or withholding of the intervention is not performed by researchers, but occurs 'naturally' in the real world due to variations, usually geographical, behavioural or environmental, that permit comparison. Because they require observation alone, natural experiments were the starting point for the more structured practices of comparative observation that are the foundation of contemporary biomedical knowledge making. Strategies have been developed to observe populations and analyse the effects of specific factors on them, that have become recognized methodologies. 'Cohort' studies, for example, are used to observe groups over time and track how exposures to various factors influence the health of such groups. 'Case control' studies compare individuals suffering from a disease (the 'cases') to those without the disease (the 'controls') in order to search for factors associated with the disease. The link between smoking and lung cancer was established by such studies, initially in Nazi Germany in the 1930s and subsequently in Britain and the United States in the 1950s.[19]

The reality of human difference is a fundamental challenge to the interpretation of the findings of these natural experiments. Are the phenomena observed in certain people due to the specific factors under study, or might they be due to biological differences amongst the involved people? To combat this difficulty large numbers of subjects can be included in the study to ensure geographic, social, and even 'racial' diversity. Large numbers allow statistical calculations to dampen the 'noise' of human variation, and to establish a 'quantitative average' and hence the biological norm it is assumed to represent.

Take, for example, the observation that heart disease is less common in southern than northern Europe. This observation triggered a search for putative causes that were quickly narrowed down to differences in diet, notably a greater use of olive oil and red wine in southern Europe that was correlated with low blood cholesterol levels and other biological factors. The rest of the story is well known: rare is the individual who has not been exhorted to eat a Mediterranean diet or has not drunk a glass of red wine relieved of guilt by its supposed positive health effects.[20] Yet a lingering question remains: is it really the red wine and olive oil that lead to Mediterranean longevity? Or might a more fundamental difference at the biological level, one not reducible to culturally patterned ways of life, be implicated? The answers to this question are likely to lie in explanations that take into account processes of biosocial differentiation that have unfolded over long periods of time, yet such processes are statistically tuned out or ignored.

While 'natural experiments' have long suggested potential factors that may contribute to disease, it was only through laboratory experiments that the actual biological mechanisms of disease causation began to be revealed and biologically effective agents were developed, such as the diphtheria antitoxin introduced in 1894 following tests on animal models. However, animal testing could not *prove* that such vaccines would actually work safely in human bodies, raising the spectre of difference once again, this time between what can be observed in the laboratory and what might happen in the real world of clinical practice. The central problem of biomedical research remained then as now: to translate findings from laboratory research – the task of which is to identify potential therapeutic agents, using test tubes, animal models and biochemical manipulations – into safe and effective agents (drugs, vaccines, surgeries, behavioural interventions, and so on) for use in patients. By the 1950s, as the historian Harry Marks puts it:

> few physicians doubted that laboratory scientists could produce potent and effective therapeutic agents. The production of reliable therapeutic *knowledge* was another matter. Laboratory scientists challenged the physician's traditional reliance on clinical experience. It took correspondingly little time for clinicians to question the relevance of laboratory studies to human disease.[21]

This tension between laboratory scientists and clinicians stimulated the development of a rigorous means for evaluating therapeutic agents before their introduction into the clinic. The growth in the development of new remedies and biomedical technologies, together with growing public anxiety about the potential toxicity of quack remedies, provided a further impetus to regulate therapeutic interventions. After the nefarious consequences of improperly tested technologies and use of drugs on human populations began to come to light (including the use of high oxygen therapy for premature babies and prescriptions of thalidomide for nausea in pregnant women in the late 1950s), rigorous testing of medical interventions intended for use on humans began in earnest. Carefully controlled comparisons between treated and nontreated subjects were deemed necessary, allowing the full effect of interventions to be observed objectively while eliminating the bias introduced at times by researchers' overly optimistic interpretations of treatment results, or by 'stacking the deck' with ideal patients.

Carrying out experiments on humans added another complication not present in animal studies, namely the placebo effect, the significance of which came to be appreciated early on in clinical research following one convincing experiment. In the 1950s it was believed that for patients who suffered chest pain because of inadequate blood flow to the heart due to blockages in the coronary arteries, tying off another artery in the chest (the mammary artery) would drive more blood to the heart and decrease symptoms. In a famous experiment conducted in 1959, patients were divided into two groups: one group of patients had a 'sham' surgery where the chest was cut open and the mammary artery was exposed but not tied off, and the other group of patients had their mammary arteries tied. Surprisingly, only 32 per cent of the patients whose arteries were tied off got better, compared to 43 per cent who received the sham surgery![22] The anatomically useless surgery was undeniably therapeutic: a clear demonstration of the placebo effect.

In developing laboratory experiments, the goal of objective knowledge was pursued by developing methods to eliminate bias that continue to be used today: (1) careful selection of control groups to ensure a good comparison; (2) randomization to eliminate bias in the selection of patients for testing; (3) 'blinding' to ensure researchers do not know which subjects receive the intervention; and (4) the administration of a placebo (such as a sugar pill) to those who do not receive the real intervention. This practice is designed to ensure that the 'pure' effect of the



intervention can be distinguished from the placebo effect brought about by believing one has received an intervention. Importantly, objectivity is assumed because social variables, including the environmental context, social support, and income, are set to one side, although even the investigators acknowledge these matters affect outcomes. Furthermore, researchers are bedevilled with another problem, namely that random events can introduce an unknown or unforeseeable factor, rendering the two groups different despite attempts to make them equivalent, and thereby confounding the comparison. The solution to the problem of confounding factors – the 'unknown unknowns' – lies in a procedural sleight-of-hand developed by statisticians.

## Taming Chance

The British geneticist R. A. Fisher, known for developing common statistical methods such as the 'exact T-test', is credited by Marks with 'embracing' chance by exploiting an until-then unknown advantage using the mechanism of randomization.[23] Prior to Fisher's publications in the 1920s, researchers could only control for factors influencing outcomes that they knew about beforehand. For example, today, researchers testing a drug to prevent heart attacks can make sure that known risk factors – such as high cholesterol, smoking and hypertension – are equally distributed in both the experimental and control groups; however, clearly they cannot do this for factors that are unknown. Randomization distributes unknown confounding factors equally amongst groups to be compared, but there is still a chance that random allocation can unwittingly stack the deck. Fisher realized that the probability of this happening could be quantified.

A powerful new technology was now added to experimental strategies: mathematical methods for detecting and eliminating bias *due to chance alone*. This is perhaps most familiar in the calculation of the 'margin of error' in political polls that predict, for instance, the popularity of a political leader (60 per cent) within a range (plus or minus 5 per cent) nine times out of ten. The uncertainty introduced by confounding factors (including biosocial differences) can be expressed as a probability value, indicating the likelihood that the results will not be valid. Such methods were not new in the world of science, having been in existence since the early twentieth century, but they had been discredited because of their use by eugenicists. However, by the 1930s a small number of British physician-mathematicians began to apply these mathematical methods to the study of disease, rather than to the quality of populations, leading to their acceptance in clinical settings.[24] The growing power of mathematical methods to 'control' for chance effectively tamed the 'wild card' of biosocial difference and laid the groundwork for the emergence of a new form of human experimentation that was guaranteed, it was argued, to give ironclad evidence.

As a result, the randomized controlled trial (RCT) became the pinnacle of biomedical research design because it appeared to be impervious to bias due to its incorporation of randomization, placebo control and blinding, all explained in greater detail below. In RCTs, the intervention to be studied is administered to one group, against which a control group is compared. To eliminate the placebo effect, the control group receives a proxy for the intervention: if it is a drug that is being evaluated, individuals in the control group receive a pill (the placebo) that appears identical to the drug under investigation but that contains a biologically inert substance. When a surgical technique is being evaluated, the control group may undergo surgery but not the specific technique being evaluated. Randomization ensures that any biological variation in bodies is equally distributed across the different groups or 'arms' of the experiment; indeed, this is why evidence from RCTs is considered to be the most valid, because the effects

produced by therapeutic agents can be rigorously separated from the background 'noise' of placebo effects, bias amongst observers and subjects, and chance events. The RCT has become the gold standard for proving that a new drug or intervention is indeed effective. As a result it is now accepted that it is statistically possible to 'prove' the efficacy of an intervention, *even without having any knowledge or understanding of the biological mechanism involved.* In this sense, RCTs perform a kind of alchemy, providing apparent certainty.

## The Alchemy of the Randomized Controlled Trial

Clinicians are all too aware that clinical trials are linked to drug marketing and that drug companies frame research questions in such a way that the answers will contribute to the marketability of their drug. While the introduction of the RCT has tempered precipitous marketing of inadequately tested drugs, current controversies around recalled drugs show that RCTs are not infallible, and have led to demands for ever more stringent testing. Given the expense of RCTs, and indeed of the entire drug development process, it is not surprising that biomedical research funded by the pharmaceutical industry is skewed towards producing drugs that will grab a share in wealthy markets, including by 'repurposing' drugs. In psychiatry for instance, trials have been designed expressly to produce results that can allow antidepressants to be marketed for anxiety.[25] Similarly, clinical trials to support new indications for existing drugs (or even drugs that have 'failed' a clinical trial) in order to expand their market share have been conducted for drugs of all therapeutic classes.[26]

In addition, a more subtle form of manipulation exists: tinkering with the actual research design of trials, including the criteria by which patients are selected. For example, rather than compare a new drug directly to its most powerful competitor, a pharmaceutical company may decide to use a clinical trial to show that their new drug is better than a weaker competitor. This process is the equivalent of rigging the World Cup so that a new team is consistently matched with the weakest team during playoff rounds, allowing it to progress to the following rounds relatively unchallenged. This can buy valuable time for a challenger drug to build a market share, with the hope that the market leader will eventually falter because of unexpected side effects. Since the statistical methods used to compare treatments are engineered to detect a superior treatment, another strategy has been to devise alternative statistical methods to demonstrate 'noninferiority'.[27] These examples show that, however accurate statistical methodologies are, the playing field where they are used is not a level one. Considerable attention has been drawn to the way in which the results of such trials are manipulated, most notably through the nonpublication of unfavourable results and the suppression of evidence of drugs' toxicity or ineffectiveness once they are marketed.[28] Sociologist of science Catherine Wills refers to these practices as the '"alchemy of the RCT", characterized by the ritual invocation of randomization and control as tools to transform ... imperfect materials into the stuff of certainty'.[29]

## The Problem of Generalizability

Clinical trials are used to compare the effects of two different interventions: a vaccine versus a placebo, or a newer drug against an established drug. However, a clinical trial cannot measure the effect of the clinical trial apparatus *itself*, the process to which both experimental and control groups are subject. The effect of the clinical trial can be due to a number of factors, including the highly selective recruitment and enrolment processes trial participants must go through before they are included. Such recruitment processes are designed to ensure a necessary level



of clinical homogeneity and sufficient cooperation to follow the rigorous biomedical regimens patients need to follow. After a biomedical intervention is 'proven' in a clinical trial, it enters the real world and is used amongst patients who, inevitably, have not been carefully selected, in places where medical care is less accessible, and in situations where the effects of the intervention cannot be rigorously monitored. In other words, the intervention must eventually be implemented without the clinical trial infrastructure, with the result that clinicians, epidemiologists, and medical scientists must constantly struggle with the problem of generalizability, or 'external validity', when making sense of trial results and judging their relevance to the problems at hand in 'real-world' health care settings.

Amongst the difficulties that arise are the following: patients who decide to enrol in RCTs – the research subjects – are known to be more motivated than those who decide not to do so, making it potentially problematic to generalize results obtained from these subjects. More 'work' is required of research subjects than of regular patients who need only attend routine doctors' appointments, because numerous visits at specific times are demanded of research subjects and more blood tests are required. This means that research subjects have to be highly motivated to be in a clinical trial and also to value the compensation – perhaps a free meal or bus fare, or even substantial sums – that is offered to volunteers.[30] Not surprisingly, research subjects are considered to be unrepresentative of patients who appear in regular clinics. Moreover, the follow-up of research subjects is better than in ordinary clinics due to the importance of collecting accurate, unbiased and timely data. Considerable effort is spent on tracking and following research subjects once the trial has ended, so research sites tend to be much better equipped and offer better medical care than do regular clinics. This trial infrastructure inevitably has an indirect impact on the care received by research subjects in trials but also, as we see below, on the communities in which they are located, which indirectly may benefit from this infrastructure.

Biomedical practitioners, epidemiologists and health activists recognize that results from trials may have limited generalizability or external validity – even when the experiment is rigorously conducted and has recognized 'internal validity' – because the subjects 'inside' the experiment are not representative of people 'outside' in the real world. The assumption that people who become subjects in RCTs could represent the general population is based largely on the idea of biological equivalence; designers of clinical trials assume that local contingencies can be statistically modelled away when subject populations are assembled across diverse sites. Epidemiologists acknowledge this is not always the case when they distinguish between efficacy – the effect of an intervention demonstrated in a clinical trial – and effectiveness, that is, its real-world effect that is often less than would have been expected.

Differences between the RCT's controlled environment and the settings of ordinary clinics have an important impact on therapy. Because patients, by definition, are not vetted as are trial participants, they may be more ill or likely to have other diseases, take medications of various kinds that interact with one another, or be less disciplined in taking their medication. In addition, in many parts of the world, health care facilities cannot deliver medications properly and local health care practitioners commonly assume that local biological variations affect outcomes. These variations can include nutritional intake, immunological status, genetic predispositions and culturally informed expectations about the body in health and illness.

Common medications used in the treatment of arthritis and diabetes have recently been subject to controversy after showing more harmful side effects when used in the general population than those detected in clinical trials, in all probability because patients are more ill than are RCT subjects.[31] Learning from what happens *after* interventions have been implemented has become an important extension of RCTs. In phase IV clinical

research, or 'post-marketing surveillance', as it is known, data on the effects of drugs are gathered after the drugs have been approved and put into regular use. The importance of post-marketing surveillance lies in its ability to detect significant side effects or toxicities not visible in a clinical trial, in an effort designed to bridge the world of experimentation and that of the clinic. Drug recall is now recognized as an unavoidable outcome of the marketing of certain drugs, with enormous loss of profits to the pharmaceutical companies involved, highlighting how clinical trial results do not 'translate' into predictable real-world effects. This is in all probability due to significant biosocial differences between clinical trial and real-world populations.

## Medical Standardization and Contested Evidence

The power of the RCT is reflected in the firm belief that biomedical practice must be informed by 'evidence' derived from RCTs or related scientific studies, a belief that gave rise to the evidence-based medicine (EBM) movement. While the RCT originated with awareness that observation alone was not enough to detect potential harmful side effects from biomedical interventions, EBM was part of a broader shift in the culture of expertise within biomedicine.[32]

The rise of EBM occurred in the wake of the counterculture movement of 1960s North America, a climate in which the burning task of the moment was to 'question authority'. The birthplace of EBM was the Faculty of Medicine at McMaster University, located in the gritty Canadian working-class city of Hamilton, famed for its steel mills. A small group of epidemiologists led by David Sackett argued that patients should no longer accept the claims of medical expertise maintained by senior physicians based on experience and anecdote alone. This was the golden age of modern epidemiology: smoking had been proven to cause lung cancer using rigorous 'case control' studies, and RCTs were believed to reliably evaluate the efficacy and safety of drugs in the wake of scandals where dangerous drugs (such as thalidomide, which causes birth defects) had been widely used without proper evaluation. Risk factors for other diseases were being revealed one by one, following on the landmark Framingham Heart Study, which identified risk factors for cardiovascular disease. Old taboos were being broken: authority could now be questioned on the basis of new research methods, and it seemed possible to have a truly scientific medicine based on objective analysis of the evidence. Today it is easy to forget how emancipatory this claim was, made back in the days when medical practice was not only paternalistic but also ridden with homophobic and racist assumptions.

It took another decade before EBM found a broad audience, in this case, in health policy and management circles. EBM was an obvious starting point for policymakers and managers seeking to rationalize costs in an era of shrinking budgets. If the US Food and Drug Administration (FDA) was the 'launch customer' for clinical epidemiology, the EBM found its institutional home in the US Office of Technology Assessment, and its equivalents elsewhere, such as the UK's National Institute for Health and Care Excellence (NICE) and France's Haute Autorité de la Santé (HAS). EBM brought the tools of clinical epidemiology – the science of causes – to bear on the minutiae of clinical practice. Not just drugs, but just about everything that was done in the clinic could now be rigorously evaluated. How many wipes should be done with an alcohol swab before inserting a syringe? What signs of foetal distress should trigger a decision for a caesarean section? Should patients sit behind the physician's desk or beside it? Clinical reason – making decisions based on a mix of feeling for the patient, past experience and textbook knowledge – gradually gave way to epidemiological reason: decision-making



driven by quantitative data, protocols and algorithms. Epidemiological reason, as a style of thought, indexes the trend whereby epidemiological calculations of risk have expanded beyond the purely actuarial to inform myriad policies that regulate our lives. Moreover, as we have seen in the discussion of medicalization in Chapter 3, such calculations gradually colonize our consciousness, borne by health messages and everyday popular culture. To the extent that epidemiological reason informs who we are and what we do, it is a powerful mode of governmentality and integral to biopolitics today.

A recognized need for EBM also acknowledges the limitations of the RCT, as discussed above. As the anthropologist Helen Lambert notes:

> not all diseases and clinical interventions have been or can be studied by an RCT. The uneven availability of such research 'evidence' can give rise to bias within biomedical policy and rationing decisions by favouring those types of clinical interventions for which the best RCT data exist. By their design, complex and population-based interventions (such as nutritional supplements for pre-school children from low-income families) are less likely to be substantiated by evidence from clinical trials than simple, individual treatments (such as a new drug).[33]

The rise of EBM over the past 20 years is based on the assumption that this approach would improve the rational and efficient care of patients, and give support to governments and health care insurers eager to contain medical costs:

> Proponents of EBM took the logic of the clinical trial and promoted it further. Essentially, supporters of EBM identified and traced the passage of medical evidence from the scientific experiment to clinical practice. This involved not only the trials that produced evidence of effectiveness but also synthesis of this knowledge.[34]

EBM marshals facts into hierarchies – with evidence from RCTs at the top, followed by other comparative approaches such as case control studies, observations from epidemiological studies of cohorts, and clinical expertise – and synthesizes them into 'practice guidelines' in the form of algorithms and rules by which actual biomedical practice comes to be grounded in scientific evidence and systematized. EBM has been criticized by doctors who argue for the importance of the art of medical practice and who contest the devaluing of clinical experience.[35] The ability of EBM to improve individual health has also been challenged by those who argue that the problem is not a lack of evidence, but the unwillingness or inability to apply evidence-based results due to political, economic and/or social reasons. For example, reluctance to abandon the use of the foetal heart monitor during labour,[36] overprescription of drugs, and resistance to hand washing are just three of the examples where biomedical practice remains stubbornly resistant to change, despite strong evidence that such changes are needed. The growth of 'operations research', which uses epidemiological methods to identify how evidence is (or is not) put into clinical practice, shows that concern about an apparent resistance to change in various aspects of medical care has recently gained currency in the biomedical research community. EBM is also contested by those who question why only certain forms of evidence (that is, quantitative and not qualitative) count, and these critics point to the limitations of the kinds of evidence that are made use of, as we have seen above in the case of RCTs.[37] Moreover, RCTs by statistical design 'control away' potentially significant biological variation. As a result, in addition to differences being made invisible amongst people 'inside' and 'outside' clinical trials, cohort studies and other sites of clinical research, so too have differences amongst people who live in different locales 'disappeared'.[38]

## Anthropological Perspectives on Clinical Trials: The West African Ebola Epidemic

In developing countries, medical anthropologists are frequently enlisted to assist in clinical trials. For biomedical researchers, the logistical difficulties of conducting a clinical trial in a developing country are compounded by the challenge of recruiting and enrolling people who live in impoverished conditions and, as a result, have often had little access to education or experience of biomedicine, and who are likely to view biomedicine through the lens of historical and personal experiences and cultural traditions that differ from those of researchers. As a result, organizers of clinical trials are often confronted with misunderstanding and even significant mistrust on the part of the populations from which participation is sought. Medical anthropologists are frequently asked to interpret the causes of such resistance and to assist with preparing suitable public outreach campaigns and approaches that foster better understanding of clinical trials amongst potential participants. When they become part of research teams, clinical investigators often call on anthropologists to analyse how the social context may affect participation in the trial, participants' experiences and even the trial results.

A revelatory case study comes from West Africa's unprecedented Ebola epidemic, which ostensibly began in late 2013 and continued through 2014, peaking in the middle of that year in Liberia, a little bit later in Sierra Leone, and finally in Guinea, and then petering out in 2015. Molecular epidemiological studies suggest that the epidemic originated in the town of Guéckédou in eastern highland Guinea, based on samples taken from a three-year-old boy who died in December 2013. His death has been deemed as the index case. Guéckédou is at the crossroads of busy trade and traffic routes that link this part of Guinea to the outside world. This region shares a common border language and cultural traditions with the chiefdoms of Eastern Sierra Leone and Northern Liberia; the Liberian capital of Monrovia is the closest port.

Ebola is a virus whose natural reservoir and host are bats. Because the disease is so infectious and lethal when contracted by a human, the epidemic had in the past always 'burned out' because its hosts quickly died. Quite likely the fact that previous epidemics had occurred in much more isolated regions of Central Africa (mainly the Democratic Republic of Congo, with some sporadic outbreaks in Uganda) where local inhabitants and health officials had learnt to look for tell-tale symptoms and to react rapidly with containment and control efforts ensured that most outbreaks were quickly contained. The recent West African epidemic was not contained, however, and would go on to trigger a global public health emergency, overwhelming health systems in Guinea, Liberia and Sierra Leone, and spilling over into Mali, Nigeria, Senegal, Spain and the United States. In Spain a nursing assistant was infected after tending to a patient, and in the United States several nurses were contaminated after caring for a patient in a Texas hospital. Isolated outbreaks in Mali and Senegal were fortunately contained; in Nigeria, sustained transmission occurred in Lagos and Port Harcourt after a patient flew into the country from Liberia. However, only eight people died, but the toll could have been far higher had not the Nigerian authorities mounted an innovative and highly effective response that drew on the expertise of polio eradication teams and IT specialists to rapidly identify and monitor people who might have been exposed. In addition to old-fashioned legwork to identify cases and their contacts, the Nigerian used airlines passenger manifests and mobile phone records to identify contacts, and monitored the situation in real time using an app they developed for this purpose. This Nigerian response is now recognized as a textbook case of 'world class'



epidemic control.[39] Ironically, despite near hysteria and constant media attention, the only country where a case went undiagnosed and caused further contamination in health care facilities was the United States.

Many theories have been advanced to explain how the epidemic occurred. Zoonotic transmission events (such as a bat bite to a human) presumably occur at fairly regular intervals, and in this part of West Africa the fact that significant numbers of people appear to harbour antibodies to the Ebola virus suggests that this is indeed the case. (An initial theory that deforestation had made bat-to-human transmission more likely has not held up to scrutiny.) Triggering an epidemic requires sustained human-to-human transmission, which clearly had not occurred in the past, a fact that militates against culturalist explanations including the consumption of bushmeat, local funeral rituals, and so forth. Increased trade and travel made possible by post-war economic growth appears the most likely explanation.

Initially the surging Ebola epidemic went unrecognized. Although Ebola is classified as a haemorrhagic fever because the infection can inhibit clotting and cause significant bleeding, in reality, relatively few patients bleed visibly. Hence, while much was made of haemorrhage as a dramatic symptom, most patients had only fever, nausea, vomiting and diarrhoea, all common symptoms associated with a range of diseases frequently encountered in the region, including bacterial dysentery and malaria. Moreover, the less lethal haemorrhagic Lassa fever is also found in the region, adding to diagnostic confusion. The epidemic was not recognized until three months after the presumed first case occurred, when *Médecins sans Frontières* (MSF) physicians with Ebola experience working in a field hospital in Guéckédou became suspicious when many patients presented with hiccups, an odd symptom associated with Ebola that they recognized from having treated Ebola patients in Central Africa. Blood was sent for testing and, because Ebola is considered one of the most dangerous pathogens in circulation, the initial samples were tested in Lyon, France, in one of the few laboratories in the world with the requisite security precautions.

The presence of the virus was confirmed on 23 March 2014,[40] and within days MSF beefed up its presence at the Guéckédou hospital. But cases cropped up in Liberia at the end of March and in Sierra Leone by the end of May, signalling an unusually widespread and worrisome epidemic, leading MSF to publicly warn of a major humanitarian crisis on 21 June 2014. Even so, it would take many more months before the epidemic was recognized as the public health crisis it really was. In the worst hit areas of Sierra Leone, Guinea and Liberia, hospitals were overrun, and by the summer of 2015 dramatic stories began to surface of patients being turned away and dying at the gates of hospitals, particularly in Monrovia. MSF was on the front line of the epidemic because it was the only organization with any experience in fighting outbreaks, honed through years of humanitarian relief work in Central Africa. By August 2015 MSF was overwhelmed and Dr Johanne Liu, MSF's international president, addressed the United Nations and called for military intervention to contain the epidemic.

Only a few days before Liu's speech, the World Health Organization (WHO) had finally declared the epidemic to be a global public health emergency, a remarkable delay that has been much criticized as evidence of troubling weakness within the WHO. The WHO's declaration triggered an international response that began to gear up in September which, it has since become clear, was after the epidemic had already peaked. Media reports pointed to US military hospitals that opened and never saw a patient. Anthropologist Paul Richards, who conducted fieldwork in eastern Sierra Leone throughout the epidemic, has argued that in fact community responses turned the tide, long ahead of the lumbering international response.[41]

## 'Jiki': A Clinical Trial Amidst the Ebola Epidemic

Ebola has no known treatment, and in the summer of 2015 the idea of conducting clinical trials to find treatments for the surging epidemic gained traction in humanitarian and research circles. Finding an appropriate agent to test was neither straightforward nor simple. WHO officials were flooded with hundreds of propositions, many of which appeared far-fetched, and had no clear process for prioritizing the candidate agents. One drug eventually became the object of a clinical trial: the antiviral favipiravir, developed by a small Japanese technology start-up called Toyama that was later purchased by Fujifilm. Favipiravir caught the attention of French clinicians and researchers working in West Africa as it had shown activity against the Ebola virus in laboratory studies and it had already been tested in humans during its initial development as an anti-flu drug. The French researchers teamed up with MSF and a clinical trial of the drug was conducted in MSF's treatment centre in Guéckédou, and eventually in three other Ebola treatment units in Guinea.

The research team included anthropologists Sylvain Faye from Dakar, Frédéric Le Marcis from Lyon, and physician-anthropologist Vinh-Kim Nguyen from Montréal (whose involvement informs the account given here). Le Marcis coined the name 'Jiki' for the trial, which means 'hope' in the local language Fula. The trial immediately confronted a range of ethical, operational, and social challenges that derived as much from the epistemological and technical requirements of the trial as the local context, which included the ongoing and terrifying epidemic. Operational challenges involved ensuring a steady supply of drugs to the treatment centres; conducting regular blood tests to ensure only truly Ebola-infected patients were included in the trial; monitoring the patients' health and potential drug side effects, and keeping meticulous records. Drugs, equipment and specimens had to be transported from airport to laboratory, but three of the treatment centres were far outside the capital, where roads were in poor condition and often washed out during the rainy season; even in the capital, chronic traffic jams could make a short journey arduous and unpredictable. And to further complicate operations, laboratory equipment drew power from the national electricity grid, notorious for its unreliability.

It is worth restating here that a clinical trial must compare two groups: one that receives the treatment and one that does not, the control group. Ideally, to achieve the strongest possible contrast, a control group is given a placebo. To avoid bias, such as placing sicker patients in the treatment group, patients must be randomly allocated to each group. Moreover, knowledge about who receives the treatment must be kept from clinicians, so that this does not bias their observations. But Ebola was not just any disease. In this outbreak, mortality was frighteningly high: as many as 90 per cent of patients admitted to the treatment units died. Even before the trial started, caregivers and community members made it clear to the trial investigators that use of a placebo was not morally acceptable.

In response to their concerns, instead of giving some patients a placebo, the Jiki trial used a 'historical control' group, that is, the trial compared treated patients with patients who were admitted before the trial started. This introduced the potential for two kinds of bias. A selection bias would have resulted if the historical control group was not comparable to the trial group because they may have been sicker and more likely to die. This could indeed have been the case, because earlier on in the epidemic patients were less well informed and less inclined to seek treatment when they initially got sick; they were therefore more sick when they sought treatment at the beginning of the epidemic than later on. A treatment bias may also have occurred, as patients in the clinical trial may well have received superior treatment than the individuals in the historical control group. This would have been for two reasons, one directly related to the trial itself, and one only indirectly. Because the Jiki trial required that rigorous



and standardized protocols be followed, patients in the trial group received more consistent care than did the people in the historical control group. This was in part because lab tests and detailed records were used to guide clinical care during the trial and because, as the trial occurred after the peak of the epidemic, patients were fewer, and it was therefore easier to give better care. During the peak of the epidemic, the period from which the historical control group was drawn, the sheer number of patients made it almost impossible, for instance, to systematically offer life-saving intravenous drips.

The moral requirement that the Jiki trial not use a placebo control group clashed with the epistemological demand for rigorous comparison, and also raised a larger ethical issue. The trial showed that the drug provided some benefit compared to the historical controls. This was considered weak evidence for efficacy given the possible biases. As a result, Jon Cohen and Martin Enserink wrote in *Science*, 'nobody is sure whether favipiravir should be used in the next Ebola outbreak'. They also quote Luciana Borio of the US FDA, who argued that weak studies 'resulted in that nebulous data zone that we were so fearful about'. Borio also stated: 'We're left with not knowing whether the product helps, hurts, or does nothing'.[42] The trial's principal investigator, Denis Malvy, countered by arguing that using a placebo was not acceptable in the setting of a deadly epidemic, precisely because the work done to address the logistical challenges was evidence enough for caregivers that the treatment might work. As one researcher involved in the study told Nguyen, what was at stake amidst this epidemic was not the collection of good evidence but demonstrating that there was an 'equality of hope'.

In the end, very few clinical trials were conducted during the Ebola epidemic due to logistical challenges, including the delays that made recruitment difficult because the trials had only started enrolling patients in the waning days of the epidemic. The Jiki trial may not have generated evidence, but it improved care for those enrolled in it. It also contributed useful knowledge about the epidemic for caregivers, who learnt to manage the disease better and who will be better equipped to handle infectious diseases from now on.

## Context of the Clinical Trial

In Guinea, decades of authoritarian rule were supported by foreign powers eager to mine the country's abundant mineral resources. When the epidemic struck, people's historical mistrust of government and foreign agents complicated efforts to contain the epidemic, which included sending out burial teams to scour neighbourhoods for bodies, blaming populations for spreading the disease, and hectoring citizens who expressed scepticism. These heavy-handed and poorly explained interventions fed cycles of suspicions and rumours that at times descended into violence. Endemic corruption made citizens concerned that the significant resources being allocated to combat the epidemic were being misappropriated, which was indeed often the case. Some even believed that public health teams were deliberately spreading the virus. In a dramatic incident, eight outreach workers were killed in the village of Womey. The sheer speed and scale of the epidemic made it difficult if not impossible to build trust and adequately explain a frightening disease, which requires considerable time and effort. As the number of cases built up, the chilling dramaturgy of the epidemic – with disinfection and burial teams appearing after each death – only made this work more complicated. Moreover, the microbiological requirement that highly infectious bodies be rapidly disposed of, along with public health authorities' fears that family members would want to reclaim bodies of loved ones, led to victims being buried in unmarked graves, feeding rumours that bodies were being used for nefarious purposes.

The inability to properly mourn the deceased, Frédéric Le Marcis notes, triggered a secondary epidemic of haunting: as the bereaved were visited by the spirits of their relatives who, because they had died of Ebola, did not receive proper burials.[43] Yet, curiously, fear and mistrust were less of a concern for the implementation of the Jiki trial than might be expected, probably because the usually sinister association of clinical trials with experiments on unwitting patients was diluted by the enormous panic surrounding the epidemic. Ultimately the trial highlighted three issues that had already been identified by anthropologists working on clinical trials. The first involves evidentiary disputes over 'what counts' in a clinical trial. The second involves the ethical misrecognition that occurs when a universal evidence-making machine confronts local realities marked by powerful political, economic and social inequalities. The third involves the social arrangements necessary to ensure objectivity that embed clinical trials in moral economies and in fact produce social relations (or 'trial communities'). To these three, we add a fourth, more explicit issue: how trials contribute to biological differences between groups, that is, those included in trial apparatuses and those not. We now delve into these concerns further.

## Globalizing Clinical Research

The Jiki trial, despite its exceptional circumstances, reflects a historical shift towards the conduct of clinical trials in the global South. Three related developments have contributed to the globalization of clinical trials. In many instances, it is today cheaper and easier to conduct such research 'offshore', where the 'right kind' of human subjects can be recruited faster and with less effort than in the United States or Europe, and where overhead costs of labour, use of facilities, and so on, may be several orders of magnitude less than in the industrialized West.[44] In a related development, a global medical tourism industry has flourished that provides offshore biomedical services at low cost. Finally, the growth of massive global health programmes in infrastructure-poor developing countries executed by local governments, NGOs, and relief organizations has created a strong demand for the identification of the most effective therapeutic interventions in such situations – the Jiki trial fits into this last category.

The growing appetite for evidence of effectiveness has brought about a remarkable situation in which participation in research is not only assumed to offer better care but is often the only way to obtain access to medical care in many parts of the world. This situation arises when trials are conducted in settings where most care is either unaffordable or unavailable, or is undesirable because of poor facilities and poor or even hostile service. Clinical and intervention trials increasingly conducted in Africa and South Asia enrol impoverished people who are ideal experimental subjects because of their poor health or high risk of disease. As a result, biomedical knowledge is derived from populations whose life circumstances – and, we would argue, whose biology – are significantly different from those who will benefit from the resultant knowledge. Testing biomedical technologies on populations who are not the same as those who will use them constitutes yet another kind of experiment. Development of pharmaceuticals is a critical nexus in these practices.

The global expanse of clinical drug trials illuminates a little-known aspect of the contemporary global economy. Adriana Petryna was one of the first anthropologists to draw attention to this phenomenon, which came to her attention during her research on the effects of the Chernobyl nuclear disaster in the Ukraine, where she noticed an astounding growth in pharmaceutical trials. Petryna points to how this worldwide expansion has been driven



by a number of factors, including regulatory frameworks that require RCT data to license drugs and the relative financial savings gained by setting up clinical trials outside the major industrialized economies. Another important factor is the growing difficulty of recruiting 'naive' patients (those who have not been treated with medications for the condition under study) in North America and Europe. For example, a person with hypertension who has never been treated with hypertension drugs would be a 'treatment naive' research subject. The disease is assumed to exist in a 'pure' state in such a subject, compared with patients whose hypertension has been adulterated by previous drug therapy, making the 'noise' of prior interventions difficult to isolate from the 'signal' of the drug under study. Originally focused on the 'second world', the notable countries of post-socialist Eastern Europe, where Petryna did her initial fieldwork, the geography of clinical drug trials is expanding, particularly to developing nations with sufficient biomedical infrastructure to support them in Latin America and Asia.

Much anthropological research has documented how many people enrol in clinical trials with the assumption (often correct) that they will receive better medical care.[45] Petryna refers to this matter as 'ethical variability' to underline how the outsourcing of clinical trials relies on landscapes of constraint that are not taken into account.[46] She points out that a globalizing political economy has created a terrain in which the bodies of poor populations are made available for clinical experimentation, and that although those who participate benefit by receiving health care while part of the trial, they are unlikely to be wealthy enough to afford the drugs that are eventually marketed after being approved. While arguably in the real world of clinics and doctors' offices there is always a degree of 'ethical variability', Petryna notes the paradox of arguing that clinical trials are a social good when the recruitment of subjects indirectly results from socially undesirable conditions such as poverty and dysfunctional health systems. Her work highlights the role of anthropologists in forcing consideration of the broader social forces that alter the foundations on which the rules of ethical research are constructed. When those who enlist into clinical trials do so because they are poor and do not have access to health care, they are likely to be from a different social group than those who will benefit from the interventions being tested. Those social differences likely also translate into biological differences (see Chapter 13) which would undermine the grounds of biological equivalence on which biomedical research is based.[47]

In some cases the vulnerability of trial participants is overtly at stake when testing interventions meant to address those vulnerabilities. Trials of pre-exposure prophylaxis for HIV using antiretroviral drugs, for instance, were seen as a way to empower women with a technology that was (unlike the condom) controlled by women. But paradoxically, when the trials failed, activists were blamed for raising ethical issues and the women in the trials were blamed for not taking the drugs properly.[48]

The Jiki trial highlights one of Petryna's key points, that:

> in 'zones of crisis', protection and safety considerations are weighed against immediate health benefits or the knowledge to be gained. Ethics and methods are modified to fit the local context and experimental data required ... 'Ethical variability' becomes a core value and a presumed course of action.[49]

The disputes over whether the use of placebo control groups is acceptable or even ethical in the context of a rapidly spreading, highly lethal epidemic highlight this nexus of variability, where local context requires trade-offs between universalized bioethical demands, local views of what is just and moral conduct, and differing perspectives on what constitutes valid evidence.

## What Should Count as Evidence?

After many years of isolation, in the mid-1990s the Chinese government began to remove obstacles to international development aid in the Tibetan Autonomous Region (TAR). Vincanne Adams, a medical anthropologist who had worked in Tibet for more than a decade at the time, was asked by Tibetans to join a team of doctors, nurses, and midwives from the United States to develop a programme for training rural health care workers in 'safe motherhood.'[50] The local government, very aware that maternal death in childbirth was taking a heavy toll, was eager to obtain whatever assistance they could to improve the situation. The group of Americans planned to introduce a midwife training programme and sought out funding to do so. In order to obtain support, Adams and colleagues were obliged to develop a 'statistically robust' project that would be comparable with data being collected from projects in other countries. They were told in no uncertain terms that they could not use maternal mortality as a measure in this research because 'not enough women die in Tibet to get a good power calculation.'[51]

Adams and colleagues could not dismiss this criticism as simply heartless because evidence-based guidelines demand that maternal mortality aggregates be made on the basis of deaths per 100,000 live births – something that would never be possible given the size of the Tibetan population. Adams asks rhetorically, what 'sort of epistemic imperative' could possibly turn a statement about not enough maternal deaths into a 'true fact'? She adds, this statement 'felt like a lie', given that proportionally 40 times as many women die in childbirth in Tibet as compared to the United States.[52] Adams's group was told that they should instead look at infant mortality, given that the number of newborn deaths was high enough to produce 'good statistics'.

The project was also chastised for not being able to find a reliable control group. Because all rural health workers meet at the country headquarters of the research project every few months for training and a review of skills, it was argued by potential funders that there would be 'cross-contamination' and interventions would 'leak' over into those communities designated as controls. As Adams puts it: 'the desire for scientific rigour in our project, in effect, aroused a need to reproduce a laboratory-like situation in which we could designate a "study population" and treat it as if it were stripped of all features that did not pertain to the discrete variables we were measuring'.[53] Adams takes issue with the assumption that careful project design would result in the bodies of women being decontextualized so that they could then be reliably treated as nondependent variables. In Adams's estimation, this production of 'facts' out of context[54] led to the 'erasure' of a population of people that desperately needed good medical help.

This particular case also illustrates another difficulty in the globalization of biomedical experiments, that of problems with enumeration at the local level. Tibetan women made clear to Adams that villagers were very cautious about divulging information because they were well aware that their local beliefs about the part the spirit world plays in successful pregnancies and birth were not compatible with those of the health care workers. This discrepancy made 'truth finding' a complicated process. The research team, which included educated Tibetans, was convinced that such beliefs block the way to a more appropriate, biomedically based understanding on the part of Tibetan women about maternal death and infant morbidity. These beliefs, health care workers argued, prevent women from seeking out good prenatal hospital-based care and are, in effect, simply lies that women tell themselves. The research team, in their certainty about their own truth claims based on numbers (their own moral orientation), could not appreciate that local beliefs are not arbitrary, but equally 'embedded in a moral terrain.'[55] For the targeted Tibetan women, the 'instruments of modernity' designed to force them to let go of 'outmoded beliefs' would strip them of morality. Ultimately this situation is, once again, a question of what counts as truth, and it shows how misunderstandings arise at the intersection of the moral economy of the biomedical experiments and that of the communities in which they are performed, even when such research addresses problems of unquestionable importance, such as maternal mortality or the prevention of HIV.[56] Similarly, for the Jiki trial investigators and participants, statistical and methodological concerns over evidence counted little compared with the urgent need to at least try to save lives.



## Economies of Blood

That the knowledge produced through clinical trials is 'pure' or 'untainted' by local context is increasingly difficult to maintain in light of historical and anthropological research on clinical trials. These findings have consistently revealed that moral economies are inevitably implicated in connection with research on human subjects. Such moral economies are most visible in developing countries where trial formats routinely exchange blood and bodily substances for medical care. While the transactional nature of clinical trials is not always visible to researchers, the social relationships that develop in clinical research are consistently viewed by participants as a kind of economy, as one informant explained to anthropologists working in the West African country of the Gambia:

> The Medical Research Council takes blood from healthy people and sells it ... When one joins the ... study, they will take much blood and if you are not lucky the [study participant] may die.[57]

In this study, Fairhead and colleagues observed how the research workers' research practices intersected with local understandings of blood and vitality, what the authors call an 'economy of blood.'[58] Their reports echo similar observations reported by others in many other parts of the world. As mentioned in the previous chapter, historian Luise White tracked 'vampire rumours' in East Africa that located Western biomedical practices within a broader economy of extraction and exploitation.[59] A veritable global economy in blood and body parts does indeed exist, making such rumours even more trenchant. Rumours about the extraction and sale of blood and body parts reflect how biomedical technologies are perceived and influence the way they are used. A moral economy of medical research becomes solidified when entire communities are routinely settled in an uneasy coexistence with a research apparatus that gives jobs and economic incentives, even as it takes blood and other bodily samples. In some cases, the moral economy of research is clearly visible, particularly when wealthy research institutions build gleaming, high-tech research compounds in the midst of impoverished communities that may not even have a reliable supply of electricity or running water. But anthropologists have discovered moral economies at the heart of medical research even in the United States where 'human guinea pigs' make a living by participating in clinical trials.[60]

The compelling lessons from this growing body of ethnography are threefold. First, the notion of a 'scientific moral economy' advanced by Daston and Gallison (see Chapter 2) is only possible where robust social relationships exist that enable trust and accountability amongst persons. Second, clinical research involves forms of exchange in which the worth of the project and appropriate compensation for participants is liable to be a constant source of tension, negotiation and resentment. And third, working misunderstandings, or even deliberate misrecognition about the inequalities and vulnerabilities that drive many subjects to participate in research are implicated in numerous research settings.

These ethnographic studies highlight a further paradox associated with clinical trials. While the authority of the evidence that accrues from them derives from procedures to ensure 'objectivity' (such as blinding and randomization), creating such conditions is not possible without a tissue of social ties, reciprocal obligations, working misunderstandings and material and symbolic exchanges already in place. Two apparently irreconcilable moral economies intersect during such trials: first, that of science and the objectivity it prises, and second that of 'trial communities' involving the exchange of blood, tissue, and participants' narratives (such as recollections of symptoms or health-related behaviour) for material compensation of various kinds and medical care.

For many the choice is between no medical care at all or medical care that comes by being part of a clinical trial. Neither altruistic nor brute exploitation, these trials enable transactions between the powerful, their intermediaries and the powerless. Anthropologist Kris Peterson argues that ethical practice requires recognition that trials may have important social consequences that transform the lives of both research subjects *and* those around them, and that researchers should act accordingly.[61] But such consequences are often 'misrecognized' because they occur long after the trial has ended, and outside the frame within which the research is conducted. Multiple ethnographic studies demonstrate that the global apparatus of biomedical research, particularly clinical trials and other experiments that enrol populations, relies on highly localized social relations that enable an economy of the gifting of blood specimens necessary to the production of evidence, and these social relations persist long after experiments end. Importantly these relations condition access to biomedical care and other resources that may in fact produce biological differences between those they include and those they exclude.

Research subjects may be biologically and socially different from those to whom the evidence from the trial is to be applied, a fact that is most visible when evidence from trials in India, for example, is used to prescribe drugs in Sweden. But it also occurs even when they are in the same geographic locale, as when results from studies are applied to populations that have not had the benefit of the benevolent health stewardship offered through participation in clinical trials. We turn in closing to further examples of how clinical experiments may produce biosocial differences, transforming individual bodies and whole social groups as they gain access to powerful medicines.

## Experimental Communities: Social Relations

In the 1920s a leper colony was established by the French colonial physician Emile Marchoux on the outskirts of Bamako in the colony of French West Africa. Marchoux was one of the Pastorians described in the previous chapter, and was trained in the emerging science of microbiology at the Institut Pasteur of Indochina. Subsequently, he was charged with founding the first African microbiology laboratory in Saint-Louis, in what is today Senegal. His interests eventually turned to leprosy and he founded the Institut central de la Lèpre some 20 kilometres from Bamako, capital of the French Sudan. Marchoux was a humanist, and did not seek to control the ravages of leprosy by forcibly rounding up and quarantining lepers. Rather, he sought to attract lepers to the *lazaret*, as leper colonies were called, with the promise of humane treatment. Marchoux's approach was a successful one, drawing in many who had been ostracized from their communities. However, treatment at the time was largely ineffective, and those who flocked to the Institut for relief became a willing group of experimental subjects when the Institut's scientists tried out new treatments in a quest for a cure for the stigmatized disease. The leprosarium



was renamed the Institut Marchoux in 1935 and continued to experiment with new agents as possible treatments. The historian Eric Silla has chronicled how a community of lepers and their families grew up around the Institut, as patients intermarried and settled around the grounds of the facility. Gradually this community became the small town of Djikoroni, which has since been swallowed up by sprawling Bamako, becoming one neighbourhood amongst many in the city, but distinguished by this particular, biomedical history.[62]

Seventy years later in the same part of West Africa, in the mid-1990s, two large clinical trials were carried out to test the antiretroviral drug AZT for the prevention of mother-to-child transmission of HIV, one trial sponsored by the French national AIDS research agency (ANRS), and the other by the rival US Centers for Disease Control (CDC). The French study tested 14,385 women in Bobo-Dioulasso (Burkina Faso) and Abidjan (Côte d'Ivoire), while the United States study tested 12,668 women in Abidjan. All the women received state-of-the-art counselling before their HIV tests. Of the more than 27,000 women tested, 3,424 were found to be positive. However, in the US study 618 HIV positive women never returned for their results and post-test counselling; in the French study the figure was 648. Researchers told Nguyen that the dropout rate was lower amongst HIV negative women, suggesting that women suspected they might receive a positive diagnosis and decided not to return for results. Of the HIV positive women who returned for their results, only 711 were included in the actual trials; the remaining 1447 women were either excluded for reasons described below or simply did not consent.[63]

The trials had an enormous impact in shaping the local population's early response to the epidemic, simply because of the sheer number tested at a time when HIV testing was not routinely offered elsewhere. Based on Nguyen's fieldwork with HIV-prevention and care programmes in both countries in the mid-1990s, the majority of people who knew their HIV status had learnt it by having been recruited into the trials.[64] But only a small minority of women were actually enrolled in the trials, although a very large number had been screened to have a significant pool from which to enrol eligible study subjects. There were numerous reasons that disqualified women, most usually for not presenting themselves early enough in pregnancy to receive AZT, or those suffering from anaemia, which could be dangerously worsened if they received AZT. Women who had tested HIV positive but were not eligible to enrol in the trials complained bitterly that they had been 'discarded'. They resented their lack of access to what they perceived to be panoply of services for women who had been included in the trials.

Indeed, the women who were included in the trial did receive medical care and social services that were not available to others, even if they were in the placebo group and did not receive the AZT. After having been tested, many of them found their way into community groups in search of material and social support; some even set up organizations for their fellow would-be trial subjects. The ethical requirements that informed the inclusion criteria that determined who was accepted into the trial generated a perception of injustice, which ironically laid the groundwork for a shared solidarity that would later surface when women enrolled in the trials were prioritized to receive antiretroviral drugs in the French government's first HIV-treatment programme in Africa. Nonetheless, over time, as drug access broadened and health returned to the women, the groups that grew out of the trial flourished. Some of the widows remarried, and many of the younger women went on to find husbands – some of whom they met in the groups – and to have children. Like the Bamako leper colony that became a village that later on would blend into an expanding city, these clinical trials spawned community groups whose members' access to treatment has kept illness at bay and attenuated many of the differences that set them apart in the cities where they now live.

This work shows that these globalized efforts to produce biomedical knowledge have a number of unforeseen consequences. The first is that biomedical research that enrols humans into trials or cohorts produces novel forms of social relations – what have been termed by some as 'trial communities.'[65] These forms of sociality are particularly salient in settings where they are directly linked to fundamental individual and collective vitality, notably in settings where non-existent public health infrastructure and poverty means that participating in research becomes a survival strategy. The resulting trial communities can be seen as a mechanism for producing a situated biology. Anthropologist Paul Rabinow first proposed the idea of 'biosociality' – new forms of social relations organized on the basis of biological conditions or common genetic make-up – over a decade ago.[66] Today, we see a kind of research-driven sociality as people gather together with intent to participate in clinical trials. The consequences of such forms of sociality will be a crucial focus for future medical anthropological investigations that will need to address the biosocial differentiation of those who are included in and those who are excluded from clinical research.

## In Summary

A cornerstone of scientific biomedicine – the ability to compare populations under controlled conditions – was built on the assumption that measurements of human biology could be used as a standard for comparison. Comparison requires experimentation, a virtual or deliberate creation of the conditions of comparison. Biomedicine is unique compared to other laboratory sciences in that it must experiment, at some point, on humans, and, because there are severe limits to what one can do to experimental subjects, comparison *must* be grounded in the assumption that humans are biologically similar. Today, evidence of biomedicine's effectiveness is increasingly derived from vast experiments that enrol subject populations worldwide.[67]

These populations are contemporary 'theatres of proof' where statistical technologies choreograph the performance of the experiment. Prevailing moral assumptions and political and economic imperatives, however, leave many questions unaddressed by this experimental apparatus and uncomfortable findings are often suppressed. The political and economic imperatives that drive research and that also weave culture, history and power into biological reality, as described in the ethnographic examples in this chapter, remain hidden from view. However, what is 'proven' in these studies determines how diagnoses are made, how medications are prescribed the world over and even informs the policies of governments and other large institutions.

The kinds of people who make themselves available for experimentation, however, are likely to be biologically different from those who have no pressing need to subject themselves to clinical trials, undermining the grounds of comparison that would enable the generalization of such evidence. Based on data from trials, interventions are being rolled out across the world and entire populations made subject to them, even though the real-world setting in which these interventions are carried out is completely different from the laboratory of the clinical trial: this too is an experiment.

Biomedical research underwent a fundamental shift when theories of biological universality converged with practices that generated knowledge by means of comparison. Once biological standards were accepted, it became possible to compare bodies, and then groups, using statistical techniques. Arguably we are at the apogee of 'evidence-based medicine', as research



progresses, financial constraints, and growing public awareness tighten the link between knowledge and practice in the spheres of clinical and population health. Clinical trials generate the most powerful forms of evidence, and are undergoing growing anthropological scrutiny. Anthropologists have contested clinical trials' evidentiary supremacy, showing that they cannot claim to be 'objective' but in fact are shot through with moral claims and are the product of political circumstances. Moreover, ethnographic scrutiny of clinical trials points to systematic forms of ethical misrecognition whereby social and biological difference is conflated and depoliticized. And finally, clinical trials actually contribute significantly to producing social and biological difference amongst humans.