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The ethical scientist in a time of uncertainty

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SUMMARY

All of science takes place amidst a world shaken by uncertainty, social and political upheaval, and challenges to truthful testimony. Just at the moment in which increasing control over biology has been theorized, our social world has become increasingly contentious and its values more divisive. Using the example of gene drives for malaria control to explore the problem of deep uncertainty in biomedical research, I argue that profound uncertainty is an essential feature. Applying the language and presumptions of the discipline of philosophical ethics, I describe three types of uncertainty that raise ethical challenges in scientific research. Rather than mitigate these challenges with excessive precautions and limits on progress, I suggest that researchers can cultivate classic values of veracity, courage, humility, and fidelity in their research allowing science to proceed ethically under conditions of deep uncertainty.

THE WORLD OF UNCERTAINTY: A CASE STUDY

Consider J.B.S. Haldane, his pipe between his teeth, there is a ghost of a smile. He is a modern man, sure of his position, his Oxford firsts in classics and mathematical modeling, and his lectureship in biochemistry at Cambridge. He is the smartest man in a generation, a polymath. He has fought in the Great War, emerged as a captain ("the best and dirtiest soldier I have ever known," according to his superiors.) Unlike many in his generation, he is an optimist. Haldane knows the danger of guessing at the future ("One can be quite sure that the future will make any detailed prediction look silly," Haldane, 1985) but is confident that scientists are just better at it. ("An actual research worker can perhaps see a little further than the most intelligent onlooker" Haldane, 1985). He is smart about malaria and figures out that sickle cell and thalassemia are genetic mutations caused by pressure from the malaria parasite long before he can prove it. But he cannot know and cannot understand how modern molecular genetics works, for in 1927, all his certainty is speculation, clever, informed, but a fantasy. In his essay, "The Future of Biology," he imagines a world that in many respects anticipates ours. But it does not. He does not know that the twentieth century is rushing toward him in all its chaotic deadliness. He does not see that a second war will be far more catastrophic than the first, or that science would be perverted, his beloved field of genetic research the very locus of the genocidal rationale for the Final Solution. He is the quickest mind of an entire cohort of scientists, which is, he writes "at present...in a stage of measuring and waiting for the idea…one man is measuring the length of feelers of 2,000 beetles…" and yet he believes that "tomorrow it looks as if we should be overhearing the conversations of bees…" (Haldane, 1985).

Haldane's great faith in 1927 was in the then-new research in genetics. He anticipated that humans would create embryos, clone them, alter them, and he thought this would go well. Haldane is so very sure of himself, and in so many cases, wrong. His vision, we can see in hindsight, is framed by his political stance, his social location, and his faith in science itself. Measuring will lead to knowing, knowing to technologies of manipulation and repair. Humans were perfectible, the languages of insects knowable.

In a recent book about the history of science, *The Knowledge Machine: How Irrationality Created Modern Science*, Michael Strevens, a philosopher of science, describes what Haldane considers a central dogma so unshakeable that he can act as its prophet. Strevens describes modern science beginning after the separation of church and state, and after the "grand gestures," "deep games," and "expansive systems" of earlier systems of natural philosophy, which were abandoned in favor of data. The collection of data and the agreement about how to collect it would prove enough about a system to validate a theory about how something worked and how equations could be produced that predicted this observation, and the question of why it existed would be set aside. Strevens calls this the "Iron Rule" of science (Rothman, 2020). This practice both limited and freed scientists, for the "measurers and the waiting" became critical to the enterprise. However, it is also not the case that a collection of data will necessarily add up to certain knowledge of the thing itself, as we see from Haldane's cheerful claims about immortality or humans grown in vats (Haldane, 1985).

The Iron Rule prioritizes the collection of data and, inductively, moves from data to rule. Nothing is certain, posits Strevens, unless it is description, enormous datasets, and careful and meticulous description of experiments that can be agreed upon as validating. He argues that the Iron Rule means that the scope of modern science would narrow the gaze to what could be absolutely seen over and over again from earlier projects of natural philosophy, in which grand theories of everything were proposed. Certainty was waiting. Certainty was replicability. The Iron Rule, however, is destabilized by a closer gaze. We know

Box 1. Glossary

Ontological: refers to the study of the nature of being.

Aporetic: a Greek word meaning "a trackless waste of sea," it is a condition of doubt and uncertainty. The image to keep in mind is of a sailor navigating the sea, on a cloudy night, where there are no paths. "Pathlessness" is another way of defining this term.

Regnant: the ruling or dominate belief.

Ipseity: the term for our essential self, our very essence, our subjective sense of I-ness.

Plight/plightedness: having a certain condition, or fate.

Epistemology: the discipline within philosophy that studies the nature and origins of knowledge and methods of inquiry.

Standpoint epistemology: the view that one's race, class, gender, or life history places them in a position to understand and know the world in particular way.

The Other: means both the particular other person or all that is in the world as non-self.

Derrida, Jacques (1930-2004): French philosopher known for work in phenomenology, developed important concepts about language and argued for the concept of aporia as central to our experience of ethics.

Virtue ethics: currently one of three major approaches in normative **ethics**. It may, initially, be identified as the one that emphasizes the **virtues**, or **moral** character.

Totality: the merging of the self into the ordinary, routinized external world.

that data are "cleaned up"; that choices are made in what is made notable; that publication limitations themselves shape reportage; that only certain observations are, *a priori*, established as important; and that phenomena are complex, occurring in nearly but not perfectly observable patterns. And we are aware that it may well be our capacity for pattern making that is behind even our most objective results. To be a scientific researcher after modernity's many challenges—Freud, Marx, Beauvoir, and DuBois—is to be aware of how little we know not only about the observed phenomena but about the observer as well. This deep uncertainty, even about data, creates a world far less iron-clad than it is supposed. The problem of uncertainty in clinical research is even greater for, of course, human research must be research on, well, fragile, changeable humans with character, agency, and will, but it is a feature of all research, even ones where the new precision of CRISPR and TALENS and CAR-T cells hold such power. We are aware at all times, if we are honest readers of science, of the vast chasm of the unknown, and not just peripheral things, but things that are central to understanding basic processes and etiologies, the unknown world so much vaster than the known world.

INTRODUCTION TO THE PROBLEM: UNCERTAINTY AS PATHLESSNESS

We live in an extraordinarily uncertain time, in a world where, despite increasing evidence of cumulative mastery—cell phones, the internet, microwaves, monoclonal antibodies—there is, revealed more sharply since the coming of the pandemic of COVID-19 and the tumultuous events of 2020, an increasing sense of stochastic disorder, a generalized sense of bewilderment in the larger public community, a loss of certainty in norms and truth claims made by experts, and a questioning of scientific testimony (Funk et al., 2021). In the United States, of course, the election and the attempt at insurrection were in addition to wildfires, darkened skies, floods, and hurricanes all at record levels, in addition to the pandemic. Worldwide, the collapse of economies and the coming of Brexit potentiated the sense of disorder. Running in parallel in academic circles, there is a realization that for all of the refinement in our understanding about how the world works, all of the fine-grained control, the elegance of molecular biology and genomics, there is far more unknown than known, and our ordering and our control is very likely to go awry at any time. For scholars of medical research, this can be said to be expected, for science famously is what can be falsified and thus disproven (Popper, 1959), which means that much of what is known will be proven incorrect, and this quality of research means that our knowledge base is constantly mutable. By design, premises derived from evidence change as evidence changes, however disconcerting this may be in practice. This is not a new insight, yet however rigorous our method, however committed one is to its variables, a life of science still appears to be one of predictability, orderliness, and surety, and it is this very stability that is now at stake. It is difficult enough to find quotidian epistemic ground in ordinary, secure eras, but in the time of pandemics and deep social divisions about values, the work of scientific research—testimony, published text, the workings of the observable biological world, and truth claims—has taken on the quality of an ontological problem (Box 1). As our control grows, as the theories of genetics unfold into practice, the practices themselves are challenged. Even more, when this takes place within the landscape of social cohesion, it is difficult, but when the landscape is also riven with serious disputes about values and worth, power and purpose, and questions of race, gender, and class, the challenges intensify. Even the remarkable—mRNA vaccines made in 10 months—takes place in a deeply uncertain world.

We all live in an aporetic condition, a landscape without a clear path forward, a complex puzzle, in which we do not agree on the events and lessons of the past, the interpretation of our present moment, or the reliability of the future, all of which were the historical, foundational ground on which our regnant of certainty rested (Rudin, 1953). Yet the aporesis of science persists. We cannot know the next event, all that is other and yet to be discovered and measured and theorized. It is this very opening up of oneself to the occurrence of chance that allows, *pas* the French philosopher Jacques Derrida, "an entrance into the future…that

is the opening into experience" (Derrida and Ferraris, 2001; Anker, 2009). It is, of course, this very quality that undergirds science, the uncharted, unmapped terrain of the real, the researcher, cutting out a slow, iterative trail.

This condition is particularly vivid when considering the field of genetics, the subject of this special edition of *Cell*, newly endowed with the Nobel Prize-winning technology of CRISPR-Cas9. Genetics told the nineteenth century narrative of linear certainty, and long after scientists had a more complex concept, the public maintained the narrative frame that genetic codes are determinative of our species being, our ipseity, and it is so very common that it has crept into the speech of politics and marketing. Yet it is here where our knowledge is still so primitive, where the linear path is actually not linear at all.

In this essay, I will explore this aporetic concept of uncertainty, which exists always, in addition to the framing social instability that marks our time. Let us begin, as philosophers begin, with definitional taxonomy. I argue that there are three sorts of uncertainty that raise ethical issues in scientific research. First, there is the familiar genre of epistemic uncertainty, which is often actually the problem of incomplete knowledge, rectifiable if more research is done or if more perspectives are heard. Here, we can resolve uncertainty: the problem is knowable, logical, and can be rationally ordered. This is the uncertainty that is the subject of much of the philosophy of science, it is in part resolved by recourse to Strevens's Iron Rule of evidence, in which plausible theories can be certified by agreed on standards of experimentation and rules of observation. Second, there is what we could call technical uncertainty. Here are classic ethical dilemmas: a problem is raised and there are differing sets of moral appeals that compete for our sense of the rightness of a solution and no clear agreement on which act is for "the good" or even how to agree on the nature of "goodness" or "rightness." The uncertainty can be methodological or teleological. For example, what ought we to do when there are profound differences in how we regard the moral status of embryos, each argument rooted in foundational and ancient texts? What should we do if our research in genetics suggests that human persons are really very different in small ways that matter greatly, if this will utterly disrupt our systems of justice? We are uncertain about what to do, even knowing all the data because we do not know how to order them properly or because different actors value outcomes differently or justify them with competing moral appeals. This technical ethical uncertainty can be profound, and bioethics has spent a great deal of time thinking about how to resolve ethical conflict or to assure that rules about the minimal agreements (treating human and animal subjects well, soliciting informed consent for research, crediting authorship correctly, for example) about values we do share. Yet, beneath these problems (and the fact that they yield to programmatic, pragmatic, even political responses give us a clue that they are not irresolvable) is the deeper problem, the ontological vertigo of an as yet unknown reality, the great, vast darkness of all that is beyond our measure. This is an uncertainty that does not yield to the logic of mandated class on ethics, the comfort of moral calculus, the weighing of risk and benefit, or the precautions of a principle.

How can epigenetics really be understood? What can be done when we know that much of what we perceive as really "real" is a mental deception, given by the structure of our neurons? What can be said about the fact that it may be impossible to ever really measure a phenomenon? How can I know if one gesture that I make, say, the placement of a genetic sequence in a particular stretch of DNA in an organism, is the first small step to an inevitably unfolding process of enormous destruction? Why and how, really, did carbon-based life begin on earth? Why does targeted DNA insert itself in different and unexpected sections of the genome than expected? What is the function of the large sections of DNA that we used to call "junk DNA"? Or of dark matter? Of course, a sane and stable investigator does not normally think about such things, well beyond the scope of a particular project, for one generally lives within what philosophers call "totality," the ordinary, horizontal world, without thinking of the dizzying void beneath, but indeed, these uncertainties surround each ordinal gesture.

However, despite this fraught landscape, moral philosophers, such as myself, teach scientists that decisions can be made and must be made about proper courses of action. This is because we are what philosophers call "plighted" (Korsgaard, 1996). Our plight this: human beings are creatures who cannot *not* act—our very inaction or inability to make a choice is, in itself, a moral gesture. Thus, when confronted by a dilemma, defined as a situation in which two courses of action, each with strong but competing moral appeals, are presented in which both choices have an array of burdens and benefits and various actors who will be affected by our choice, we make a decision, and we proceed on one path or another. This is true, even when we choose not to go forward with a project—we cannot stop in the sense of returning to a time prior to the discovery, for we are "plighted," and thus we move forward in a world without the scientific concept, proof, or technology, but we move forward into a place in history all the same. Moreover, we create for ourselves a sense that there is one path forward, when in actuality, we confront only an aporetic opening.

YET SCIENCE PROCEEDS

Philosophers are intrigued with this problem, with the phenomenology of a self, encountering the world as other, with the way that each decision, endless, opens and simultaneously closes the next set of decisions, reveals and yet conceals different available futures. And while this is interesting, bioethicists and scientists are faced with practical choice. When confronted with a dilemma in which competing appeals arise to make the case for continuing research, modifying the research to address ethical concerns, or in some case, advocating for stopping it entirely, bioethicists teach scientists how to make an ethical decision and how to use a standard methodology. First, we clarify the dilemma, understand all viewpoints, master and agree about the scientific or medical facts, review the history of similar choices, consider the options, identify core values that allow you to rank or weigh them, assess, chose, justify, and proceed.

In the case of real-world dilemmas, we also have other urgent, complex puzzles with which to contend. Now that we can begin to see more clearly the systematic issues of race and gender, even knowing that we carry biased concepts is not enough: we need to ask how these have shaped our perceptions of the

both the initial issues as well as our truth claims. After the scandals in stem cell basic research, where in the elite Korean lab of Professor Hwang Woo Suk, false claims were made that human cloning of stem cells was accomplished in 2006 and the false claims about reprograming of stem cells that were also made in the case of Haruko Obokato, a researcher at Riken Center in Japan in 2014, we are aware of the possibility of deceit, recklessness, and opportunism as human phenomena—and science is no freer of these mendacities than any other human endeavor. In some settings, powerful training hierarchies or fear of professional disgrace or retribution silences junior colleagues, further distorting truthful discourse.

Underlying all research are essential premises of the scientific tradition. For example, this can include the following: that which is now unknown is discoverable; that the known builds on the unknown; that equipoise is needed for a true scientific inquiry; that in principle, there is always a confirmable hypothesis; that the nature of error is such that it is inevitable, but that it can be fortuitous, and finally, that while failure may define all early stages of research, even this failure will be turned to some larger, successful task.

Ethics, too, assumes essential premises: first, that the future can be known, and one can *rationally* calculate and evaluate moral activity on the basis of a probable world to which one can speak and evaluate. Consequentialist theory is based on this central dogma—for beneficence and nonmaleficence to work as principles requires us to prognosticate, to imagine our choices as if they would come to exist, and then consider these imaginary effects. Ethical theories rest on the idea that one can shape one's very self by activities that can be known and chosen with reason and *a priori* judgment. We act as if the past is always predictive. So—in case A, we think that we know that A → B, and then we weigh good social consequences against harms and burdens or virtuous actions as if they are cumulative. One takes "account" of risk, but rarely, of our deep inability to actually know the future—after all, our essential premise is unchallenged, that we are capable of "weighing" the future, "balancing" the outcomes, imagining that we control it. But we cannot fully know, and thus cannot really set up a plumbline.

Some of this has long been understood in research ethics, however uneasily. There are, however, fundamental problems in the central theorical assumptions behind this ethical method. Much of the moral calculus is based on a mutable knowledge base. Much of the prognostication is based on partial knowledge, because, of course, knowledge is always incomplete. Most troubling of all, much of what is most important, morally, about the future is unknowable and uncontrollable.

Ethical assessments, moreover, rested on what scientists told moral philosophers about their work. Often, we carefully read final research papers or attended presentations but did not have access to what was left out, innocently, in the first discussions about what is or is not important to consider. (Something Strevens calls "sterilizing" the work.) Often, ethicists think about genetics, for example, as it is portrayed in the popular press as a sort of cartoon, where everything works perfectly, and we accept that simplicity ("CRISPR works like a kind of scissors!"), so we can discuss things like "intent" or "implications," not seeing the instability or uncertainty in the project itself. But as Strevens points out, the problems raised by epistemic uncertainty really can be addressed by careful, if limited, agreements on the sort of experiments that could yield enough data to achieve consensus (Strevens, 2020). (When my bioethicist colleagues Leroy Walters, Jonathan Moreno, Baruch Brody, and I considered this problem as a part of our work in the Howard Hughes Bioethics Advisory Board from 2001–2007, our research uncovered a great deal of fragility in ethical decisions in scientific research, both in the clinical and the basic research setting. We came to understand that the actual process of research is framed with uncertainty: what else is unknown to us? What facts are chosen to be credited? Why is it a dilemma *now*? What about possible data error? Is the past always predictive? Can we really accurately weigh risks? What if our values differ? What about competing truth claims? What about competing risk assessments? And while some of these questions are part of standard theories in research ethics, the problem of deep, philosophical, aporetic uncertainty is far less characterized.)

In clinical research, the usual way to solve such problems of technical uncertainty is by strengthening rules about informed consent (letting the human subjects in research trials, for example, assess the risk themselves and decide whether to participate in situations of uncertainty where the risk is difficult to objectively assess). If one of the first premises in bioethics is that the future can be known and rationally shaped, the process of consent is the second essential premise, that human persons are rational actors, in possession of all the necessary facts to make a decision for themselves as autonomous moral agents, deriving from the principle of autonomy. This principle too, has problems, which have been widely discussed in the literature of bioethics (Faden and Beauchamp, 1986). Individuals do not adequately calculate risk, thinking that the odds are in their favor when they are not or that the risk is large when it is not. Faced with no viable options, dying patients may have no other choice of any action except participation in a trial. In genetic research, as it was presented to me as an ethicist member of the NIH Recombinant DNA Advisory Committee, parents were desperate to find a way to treat their children and doctors were excited about their findings and wanted to proceed with trials to prove their theory—everything aligned to make consent inevitable. But we found that there were limits to consent, no matter how well a subject is informed: what can we know, and what do we tell? What sort of information is useful and to whom? How well known do the consequences have to be in order to be ethical? How small must the risk be for the experiment to be ethical?

Uncertainties in the process include a socially evolving sense of what is "consent," what is "freedom," and what is "coercive." We came to understand that we could not know what innocent gesture or process in the research might turn out to be a critical ethical mistake when considered across temporal distance (i.e., the concern for special vulnerability was not in the literature prior to the twentieth century. Research done on prisoners is a classic example).

We know, even as we teach the doctrine of informed consent, the bioethicist's version of the Iron Rule, that our knowledge could be incomplete in multiple ways. First, we always have incomplete knowledge about the level of risk individuals and communities actually face, and it varied, we found, in different social locations because risk acceptability is experienced

interiorly to particular communities. In ethical decisions, moreover, there were always several possible outcomes, and while the probability and value of their occurring can be estimated with a reasonable degree of reliability, and rational individuals could maximize (or satisfy) expected utility, we came to understand that not only subjects but also researchers, and even oversight committees, acted rationally at times, and at others, only partially. Second, we came to see that in the cases where there was a need to make decisions under uncertainty, and where there are several possible outcomes, the probability and value of their occurring cannot always be estimated with a reasonable degree of reliability. Rational individuals may adopt different strategies for dealing with this type of uncertainty, unless one strategy dominated because of special factors, sometimes monetary ones, sometimes the pressures of research competition, sometimes the need to solve a problem and end suffering one felt deeply or urgently. Of course, informed consent norms are not the only recourse to solve this level of uncertainty, but as more research emerged by Richard Thayer and others about irrationality and decision making (Thaler and Sunstein, 2008), this norm seemed even more questionable.

Moreover, we began to understand the profundity of the issue of uncertainty, especially in genetic research, which is always a set of promises about the long future, unlike other medical interventions, beyond the lifetime of a particular individual patient. Because the logic of genomic research is linked on the logic of computer coding, the central dogma seemed to privilege certainty, and while this is no longer the case for scientists, it is still the way the lay public understands genetic intervention. The progression from DNA, RNA, and protein to trait or behavior seems to follow with inevitable logic, and we were initially urged to think of genetic manipulation as a sort of a spell check. When the genome was "fixed," it would unspool the capacity as promised, as predicted, as the instructions foretold. If molecular genetics is the deconstruction of the real into the smallest possible parts, we expected that putting the parts together would properly allow reconstruction. But it proved far more difficult, far slower, and far more imprecise (Endy, 2008). Here is where we reach the limits of what the norms provide when making ethical decisions under conditions of deep uncertainty.

Let us see how this understanding works in a contemporary example of genetic research. In this essay, I turn to a new problem, the research on malaria, and the consideration of a CRISPR modification in the mosquito vector that would be "driven" across the species of mosquito that carries the deadliest type of malaria parasite in an effort to reduce the incidence of a deadly disease, falciparum malaria. In thinking about the problem of uncertainty in the age of genetic research, where the discordancy between our mechanisms of control and our capacities for stable judgement are most evident, I will consider this limit case, the use of *de novo* genetic interventions against a disease that potentiates the deep suffering of the world's poorest populations.

GENE DRIVES FOR MALARIA CONTROL: A CASE STUDY II

Now eclipsed by our concern about the astonishing death rates from the COVID-19 pandemic, malaria historically has been one of humanity's leading causes of death (WHO, 2020). Despite advances that cut the death rate in half after a massive WHO campaign in 1955–1985, it continues to kill close to half a million people a year. Vector-borne diseases have been humanity's oldest menaces. Globally, malaria, with 200 million cases and 456,000–627,000 deaths annually, kills about one thousand people a day. The burden of malaria is most fully borne by the very poorest and most marginalized populations on the planet, areas that are also sites of ecological decline, war, or lack of stable education or any sort of reliable civil services. Children under the age of 5 are at particular risk of the worse aspects of the illness, including encephalopathy and death. Sub-Saharan Africa has the most intractable malaria problem, with both large areas of resistant disease and the most deadly species of the parasite, *plasmodium falciparum*.

Malaria has proven a difficult foe. Malaria largely occurs in remote rural regions where health care in general is hard to access, making the death toll higher. In the 1950s, mass DDT campaigns came close to eliminating malaria in most areas until a combination of public opposition to the longer-term population effects of insecticides and the capacity of mosquitos to adapt to higher levels of DDT ended the projects. Responses to malaria rest on methods developed in the late nineteenth century, bed nets, swamp draining, anti-larvae poisons, and anti-malarial drugs, such as quinine and atabrine, which were less and less adequate. Bed nets have been widely distributed, and these nets have reduced the exposure rate, but the nets need constant replacement, and are temptingly useful as fishing or hunting tools. And the parasite, in addition to the mosquito, quickly adapts and becomes resistant even to the newest drugs to treat the disease. The current drug, artemisinin, now produced synthetically, will inevitably become useless in the same way quinine became ineffective through acquired resistance by the plasmodium and the DDT became useless through the resistance of the mosquito vector. The resistance to artemisinin can already be observed in Southeast Asia despite efforts at combination therapies. Next generation insecticides, which carry their own environmental risk, only have incomplete impact on transmission, and finally, efforts to create vaccines have not been effective, are difficult to administer, and are expensive to distribute. To really eradicate malaria, new technologies in addition to the ones now known are needed. This turned the attention of scientists toward molecular genetic controls that focus on the manipulation of heredity, a genetic control method called a "gene drive."

Gene drives are naturally occurring phenomena in wild-type populations, where sometimes, Mendelian inheritance is disrupted and a genetic trait is inherited—or "driven"—with more frequency than the usual 50% odds for a genetic inheritance pattern, which is seen in all species that reproduce sexually. Gene drives change this throw of the genetic dice, as if the die were weighted in favor of a trait. This replication mechanism may not be advantageous for the organism and is usually self-correcting. But the idea can be harnessed in critical ways, given the particularities of malarial transmission: like all mosquito-borne diseases, malaria is only transmitted by older, female mosquitos, who need a meal of human blood right before they lay eggs. There are 3,500 mosquito species, only three transmit malaria, and only one of these is largely the culprit in

sub-Saharan Africa, *Anopheles Gambiae*. It is this mosquito that is the target of an effort to eradicate the malaria parasite it carries. This work is being done in a large academic co-development project, Target Malaria, between University College London, other UK and US universities, and universities in three African countries—Mali, Burkina Faso, and Uganda (Burt and Crisanti, 2018; Burt et al., 2018; Collins et al., 2019). In the case of Target Malaria, where gene drive research is most advanced, and where plans are being made to eventually deploy it, a team of molecular biologists, population geneticists, anthropologists, policy makers, and community outreach experts has been working for over a decade on the creation of a project in three African countries most affected by malaria. Target Malaria is a non-profit organization that organizes several different teams and methods and, at all times, is a collaboration between Africa and Western researchers.

Scientists in the project study whether CRISPR interventions that carry a gene coding for a sequence-specific DNA along with its cutting enzyme can be inserted into mosquito embryos so that the new trait and the method for spreading it will be inherited in a biased manner throughout the population of wild-type mosquitos. A gene drive that slightly alters the sex ratio of Gambiae mosquitos, for example, so that more males than females are born, or a drive that interferes with a female's capacity to reproduce, would over time (a mosquito generation is 20 days) reduce the number of females and reduce the biting rate and thus have the capacity to reduce transmission of malaria to near zero. This is known as a suppression drive. Other drives, with other targets, are also being studied by scientists at the University of California.

The plan for the work is iterative and intends to avoid error and harm by using containment, first in Britain, then in Italy, then in Africa, with releases of sterile males, then males with the construct for sterility but without the drive component, slowly moving toward the moment a population of genetically altered males with the gene drive is taken to a village for release in the wild. Each step is practiced, numerous safety precautions are considered and taken. However, even the safest team will err—it is in the nature of human actions—and errors in a stable world are only one problem. The more profound issue is the problem of aporesis in a stochastic world, in which any action across a mutable horizon is necessarily contingent and uncertain.

Obviously, the elimination of a dreadful disease would be a magnificent human achievement, but it does not take much imagination to pause before the risks of action in the face of the extraordinary uncertainty that surrounds this project. Against the enormity of benefit that eliminating deaths from malaria would bring should this be successful, there are questions that can be raised about possible harms. These range from the possibility of unintended consequences when a species is eliminated from an ecological niche and its food web, to the cultural and religious concerns about a technology so powerful it can interfere with the reproductive cycle of a wild species, to concerns about horizontal transmission if the target is in a highly conserved genetic region of the insect genome, one that is essential for reproduction in all species (this is highly unlikely, since the malaria parasite has been stable in only a few species, even within mosquitoes for thousands of years, yet this is a concern that has been raised by NGOs and other opponents).

We do not know what the limits of our power should be or how far we should go in the elimination of a species if the species carries a deadly organism. We do not fully agree on who can make that determination. Westerners tend to think of the dangerousness of proceeding with a new technology, wary of a history of error, but if you live in a malarial region and if you have lost child after child to wrenching fevers, you might think that blocking new technology is by far the more unethical course of action. If we agreed on the analysis of the past, we might be persuaded that since mosquito populations were suppressed before, in the sixteenth century when the marshlands of the Fens were drained in East Anglia, in the nineteenth century when the crop systems of North America and France were changed, and again in the twentieth century when first Paris Green and then DDT poisoned the habitats of *Anopheles*, and the habitats and the mosquitos rebounded without their parasites, such an intervention would be acceptable again. But we do not fully agree on the past or how to interpret or evaluate it. If we agreed on the telos, we might argue that a high risk is acceptable, but we do not fully agree on the future either or the worth of various ends. If researchers were more secure in their understanding of the genome and their technical prowess, that would be defensible as a place to begin, but the honest researcher is aware of the limits of her capacity. And while epistemic methods and rules of engagement and consent can be established to address many of the ethical challenges of the project, it is without question that the deep uncertainty, the unknowability within the scientific gesture, remains.

Should research be stopped because this deep uncertainty is fully revealed? Should it be halted while meanwhile, actual, specific vulnerable children die who might well be saved by fully funding the research and allowing it to proceed in the face of uncertainty? Are the ethical guardrails of our standard practices of research ethics enough, even if they do not really address the fundamental uncertainty? We will return to this central ethical problem.

Can ethical research be done under conditions of uncertainty?

Researchers turn to ethicists because decisions about the validity and worth of their work must be made. Yet the argument of this essay describes the nearly impossible problems associated with making decisions under uncertainty, and once the reality and scope of the aporesis is understood, one surely is drawn to ask whether it is ethical to proceed with research at all, especially projects in genetic research such as gene drives, which would affect not only a handful of children with a dreadful illness, but whole populations, regional species, and local ecologies. Indeed, some, including many in the European Parliament, and many scholars in Europe have codified the answer to this: no. In foundational EU documents, what is called "The Precautionary Principle" is a statutory part of regulations.

> The precautionary principle is detailed in Article 191 of the Treaty on the Functioning of the European Union (TFEU). It relates to an approach to risk management whereby if there is the possibility that a given policy or action might

> cause harm to the public or the environment and if there is still no scientific consensus on the issue, the policy or action in question should not be pursued. Once more scientific information becomes available, the situation should be reviewed (EUR-Lex, 2000).

The first use of the precautionary principle was made in 1992 at the UN Summit on Environment and Development (the "Rio Declaration").

Principle 15 of the *Rio Declaration on Environment and Development*, adopted by the United Nations Conference on Environment and Development in Rio de Janeiro, Brazil, 1992, states that "in order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation" (European Commission and UWE, 2017).

By 2000, the EU Commission solidified the principle, in the words of the Commission, "better safe than sorry." Necessary in situations where there is "incomplete information, inconclusive evidence, or public controversy over the appropriate response to hazardous substances or activities…regulatory intervention may still be legitimate even if the supporting evidence is incomplete or speculative and the economic costs of regulation are high." This doubled concept meant that a new principle could both block processes or technologies that carried any risk of harm and enact protective provisions even if these had not been fully tested, establishing two separate standards of evidence.

Further, the UN Commission added "recourse to the precautionary principle presupposes that potentially dangerous effects deriving from a phenomena, product, or process have been identified, and that scientific evaluation does not allow the risk to be determined with sufficient certainty" (European Commission and UWE, 2017).

The Precautionary Principle has been both attacked and defended, but that is not my primary focus. I raise it to explain why it has proven to be inadequate by sketching some objections here. Does it help us move ahead in conditions of uncertainty? I would argue that it does not, in large part because it avoids the profundity of the problem, for what we actually need to assess as we consider genetic research, is not only one proposed intervention—it is our condition itself. We will move ahead into the temporal future, for there is no escaping chronicity and there is no escaping our "plightedness." Our present, even standing still, is as racked with uncertain outcomes as the future suggested by any intervention. Any new "technology, process, or product" might threaten us, but so might stopping it. Further, choosing the particular moment in time in which we reside means choosing what we now know and have and validates it as inviolable: not only the environment but the burdens it bears, the power relationships, the implicit bias, and the pleasures of privilege that shape our assessments as well as other measures. Non-action is not safer, it simply makes the moral claim that our present situation is fine, safe enough, whereas it is actually morally unacceptable.

Return with me to the problem of gene drives and the uncertainty about the future they might bring, and one can see that concern about possible outcomes avoids attention to the desperate injustice of the present, the unfair lethality of the burden of disease on the poorest humans, and not to mention the species-killing technologies now used, the insecticides, and destruction of wetlands. We are "plighted" in this, a second way as well, that we live in a world that is full of human suffering, brokenness, and hunger—not only a place of serene order whose beauty and grace is threatened by technology. Decisions are linked to other decisions, happening and unfolding all at once, horizontally, simultaneously, and not only in a lineal fashion. Maintaining the status quo is not actually "better safe," because there is not really a safe to stand on, at least not for far too many. And with only safety and certainty to guide us on a one true road "too little in this world would change. We would live in a world closed down to the novelty of an event—a rupture always necessarily outside the limits of knowledge and current logic" (Anker, 2009).

The risks of knowledge

There are serious risks, however, to the approach I have thus far described, of seeing an aporetic uncertainty and knowing that reality is held together by the illusion of order, with constant doubt and with constant awareness of the void that surrounds any act, as any scientist getting this far in this essay can forcefully explain. I too know that risk. Following the line of this argument might lead one to assume that knowledge was simply a matter of standpoint epistemology (MacIntyre, 1981), which might be well enough for humanities disciplines, where the stakes are the judgement of literature or the worth of an argument about hypotheticals, not so very high, surely not life and death, but are utterly inadequate when it comes to scientific research. The idea that uncertainty should be understood as fundamental, the feature not a bug, can be understood by scientists to be a sort of nihilism, promoted by philosophers unwilling to turn from speculation to the serious tasks of science. There is a *real*, my colleagues in science remind me, there is a real world. This is correct.

It is important to understand that my claim about deep aporetic doubt is not merely an act of deconstruction but rather a call to the most liberatory aspects of scientific knowledge. Understanding that the future is open does not mean that truth is entirely undermined. Clarifying the reality that objectivity is difficult to achieve, that the Heisenberg effect is profound, or that attending to the complexities of epistemic doubt does not mean that nothing can ever be known, measured, or observed, for that would be taking the concept of aporesis into absurdity. But suggesting that science lives and acts in a time of great uncertainty and yet must proceed creates important and sobering moral choices. In fact, noting it and making this legible allows the scientist to remain open to possibility, discovery, and failure, a core feature of the enterprise of experiment. As philosopher Michael Anker notes, understanding that you are faced with uncertainty is not an excuse to defer or to hesitate prior to action. It means that each decision is both a response to the urgency to act and a recognition that each decision opens up a new terrain of unknowability, a new pathlessness, and a new need for a decision. "Every decision reorganizes the fabric of life, but each move in itself does not lead to a conclusive point of certainty; it

leads to a new, uncertain, undecidable, and aporetic space from which once again we must decide and act" (Anker, 2009).

Ethicists make both descriptive and normative claims. This essay is in large part descriptive, elucidating some epistemic and ontological challenges, yet I am also making some normative claims. It is the contention of this essay that if the way to think about the ethical challenges of uncertainty emerges from within the scientific disciplines alone and is focused on epistemic uncertainty, this solution will necessarily be limited and ultimately unstable. And if the deep uncertainty is ignored, and we hustle instead to create ethical codes and rules that do not take it as central, addressing only the technical aspects of uncertainty with consent, then the rules will be insufficient, little wooden bridges over the void. This is because addressing science is mutable, the world probable, the real uncertainty, vast.

Yet there is a way for science to proceed ethically. What will remain stable are the ethical commitments that call for a worthy life within conditions of immutable uncertainty, for these ever have been the subject of moral philosophy since its beginnings in the memory of cultures as diverse as scriptural discourses, Greek narratives, Confucian philosophy, Arab poetry, and Socratic debates (Strevens, 2020).

A wide range of moral philosophers understood the limits of knowledge. It is not new to know that the world is more dark than light, more unknown than known. They understood what it was to live in a time of chaos, and yet, they engaged in the robust inquiry of ethics, asking, "What is the good act, and what makes it so?," "What is the worthy life, and how might it be achieved?," and "How is the good society structured?" It is here, in the reflection on these questions, that we can consider norms for decisions and rules for how to move ahead in science in times that seem as terrifying and capricious as the pre-modern world, a world of volcanic eruption, constant war, epidemic disease, and yet, a world where philosophers first thought, "What do we mean by "justice?" and "How can one know truth?" And within this discipline, many turned to the question of virtue and how it could be named, maintained, and taught.

Decision making under conditions of uncertainty is difficult to structure rationally in the experimental context, perhaps especially when genetic research now promises so much, and perfect control seems so nearly possible. At the most technical and straightforward, it seems to require, at a minimum, adequate updated information, a process in which core values are surfaced and clarified, and protection against exploitation of vulnerability potentiated by uncertainty. All of this becomes critically important in times of crisis, ever more important in when a deadly pandemic occurs and when truth itself becomes a matter of opinions and politics. To return again to gene drives, much can be done to make science more ethically trustworthy. For example, the many proposals named by the many commissions and committees that have drawn up careful technical rules for safety, containment, iterative projects, environmental impact reports, stopping rules, publishing and licensing norms, and the structures of community engagement so important to the success of the project are useful and should be heeded. But the deep, aporetic uncertainty about the long outcomes and implications of the work will be complex, will be unknown, and will always remain so, and to promise otherwise is the wrong sort of promise.

In other words, not only is it possible to consider scientific research ethically justifiable to continue under conditions of uncertainty, I consider the recognition that uncertainty is a profound feature of science and moreover, constitutive of human freedom, is itself central to the work. As Michael Anker concludes, freedom, in the absolute sense, is the phenomena of living in a world without absolute measure. "We stand thus in the opening of freedom, in the aporia of anxious indeterminacy. What we do here, or what we do in relation to the aporia of freedom, makes all the difference in regard to how the world unfolds" (Anker, 2009).

If we are able to make truly free, and I would add, truly ethical decisions, "a decision worthy of being called a decision," we must understand that our decisions create new worlds. "Aporias thus draw us toward the possibility of ethical becoming, the possibility of living an 'ethical life' in a world without absolute measure" (Anker, 2009). It is to this "ethical life" to which I now turn to conclude.

Conclusion: the possibility of an ethical life

Can science be done under these conditions? Beyond our commitment to the rules of science and the technical utilitarianism that these rules provide, beyond even the core ethical understanding of the absolute primacy of the theo-philosophical recognition that the Other must be regarded as one's kin, both of which are imperative, let me suggest that we will need to commit to four other things if science can be regarded as ethical when so much is at stake. These are the virtues of veracity, courage, humility, and fidelity, the stable core of Aristotelian moral order. If scientific knowledge is the sort of knowledge that is constantly mutable, perhaps these more enduring attributes may provide some guideposts. In a pathless sea, we turn to the character of the crew.

First, investigators must always tell the truth without exception. This requires clarity and sincerity for everyone involved: investigator, subject, polity. We must be honest about risk, honest about the unknowable nature of the future, truthful about failure in research, and truthful about mortality, morbidity, and fragility in the clinical research context, especially when we consider the power of genetic research, for the genome is now regarded with the same degree of moral seriousness as medieval scholars considered the soul—definitional, inviolable, special. This degree of truthfulness requires humility, and it is difficult in a time of contention, but it is critical.

Second, investigators and their institutions must be courageous, risking complete failure, risking political pressure, and risking upending previous, normative structures of power. It takes great courage to challenge the hierarchies of the laboratory, for example, or to admit to the funders that a long path of research will not yield results after so promising—and promised—a start. It takes courage to defend your work in a time when there is such anger at elite knowledge, and disdain for intricacy, nuance, and complexity. It requires courage, not timidity and not rashness, for what good is aporetic freedom if one is afraid to act?

Third, the honesty about uncertainty ought to lead to a sense of humility. Science holds power: predictive power, explanatory power, and where religion alone promised salvation, medical science now does so. But scientific expertise is not necessarily generalized to expertise in all epistemologies, and researchers need to have sense of humility as well as courage for a boastful or arrogant claim has no place in the laboratory. It is the wrong sort of promise, to promise revolution or redemption. Surely, the continual surprises that have unfolded in the COVID-19 pandemic alone should render the ethical scientist humble.

Finally, if there are the wrong sorts of promises, there are the "right sorts of promises" that can be made in science, and the promise of faithfulness, fidelity, is that sort. The ends of research may not meet the telos of the concept, harm may come, and it should never be borne alone. Investigators cannot know, really, fully, or completely what their research will accomplish, for the space that is opened by research science is always an open space. Every decision leads to a new place where a new decision is called for, and "the incessant change and flux of all phenomena (whether it be named subject, object, or thing) disallows any true stability or absolute form of certitude" (Anker, 2009). A decision is made to proceed, the world shifts, and new decisions unfold within the first. For post-modern philosophers, it is this place of indeterminacy that allows creativity. The openness to possibility is the openness to the Other who might next come, the very ipseity of the future, bearing the name of the future.

But if knowing the profundity of uncertainty does not allow us to know all the implications and consequences of our work, then what makes the work ethical and responsible must be something else— and it is the promise of fidelity: that the researcher will stand by, being witness to the consequences of her acts, and taking responsibility to repair any harm they may bring. Subjects, environments, and societies are not objects that can ever be abandoned, profit taken, and damages forgotten. This is the realpolitik of that lovely philosophy of openness of inquiry as freedom of speech. Its correlate is the openness, utterness, and incessant responsibility for the Others who bear the weight of your work. This is the duty that is correlative to the freedom of creativity. This promise—this "I will stand by you"—needs to be inscribed in all of the technical norms that we write, but its seriousness must first be deeply understood. If science were not uncertain, if it were a small human activity, one could make a firm little ethics rule about how it ought to be played. But it is not. Scientific research is one of the great human moral gestures, one of the great works that is possible to us, and it is an uncontainable, unruly, yet powerful response to human suffering, and that is why it is so.

This observation and this ordering, this counting, and this experiment, in all its grandeur, anxiety, and risk, once fully understood, endures. It must also be responsible at this scale, across continents and lifetimes. This is not to abdicate the necessity to follow the regulations that we ethicists are so intent on erecting, for they are necessary, the boundaries and ligations upon which the process rests, but it is to ask for far more: how to respond to the uncertainties that surround us, to the shaken world, the wary publics, the terror of the pandemic. It is not only by the work of research; it is by the construction of the self of the researcher, the moral agency of the investigator who is shaped by the inquiry and who understands its gravity. The ethics of science in an uncertain, limitless, vertiginous time begins in the inevitability and certainty of the duty of the scientist and the limitless, endless creation of that virtuous life.

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L.Z. served as a bioethicist on the following boards: Target Malaria Ethics advisory board, NASA Ethics Advisory Board, the American Heart Association Ethics Advisory Board, the Merck Regenerative Medicine Research Ethics Advisory Board, the NIH DSMB for the PETAL (ARDS Research) Consortium, and the CDC Biological Agents Working Group. With the exception of Merck, all are unpaid positions. In the year 2020, L.Z. was paid $1,500 for Merck consultation. L.Z. is a professor at the University of Chicago Divinity School, who supports her research, and a senior advisor to the Provost for Programs in Social Ethics. L.Z. serves on the international, independent Ethics Advisory Board to the Target Malaria Consortium, an academic, not-for-profit consortium of African and Western University researchers and community members.

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