REWRITING (NON-HUMAN) NATURE[†]

HENRY T. GREELY[*]

There is nothing on earth divine besides humanity.
—Walter Savage Landor[1]

I, on the other hand, am more often tempted to consider humanity a metastatic tumor on the Earth's biosphere or, perhaps, with Stephen Hawking, as "just a chemical scum on a moderate-sized planet, orbiting around a very average star in the outer suburb of one among a hundred billion galaxies."[2] But, for all our faults, one cannot accuse our species of lacking self-esteem, as most of our traditions exalt humans above all other things on, over, or in Earth.

I have been writing about the ethical, legal, and social implications of advances in genetics for thirty years and I, too, have focused almost entirely on human genetics.[3] Increasingly, I have come to view this as a mistake, even, or especially, after publishing two books on genetics in human reproduction through embryo selection[4] and embryo editing.[5] Because of our high—and appropriate—aversion to taking risks with human babies and adults, we will

[†] This Essay was submitted as part of the *Boston University Law Review Online*'s November 2022 symposium on *Rewriting Nature* by Dr. Paul Enríquez. Online Editors Erin Beaton and Kaitlin Ostling organized the symposium, and Professors Christopher Robertson and Kevin Outterson moderated.

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[1] WALTER SAVAGE LANDOR, IMAGINARY CONVERSATIONS (FOURTH SERIES) 189 (Roberts Brothers 1883), https://play.google.com/books/reader?id=vn6pgPFkzysC&pg=GBS.PA188&hl=en.

[2] *Reality on the Rocks: Beyond Our Ken* (Windfall Films Feb. 26, 1995).

[3] Some of the honorable exceptions, including the two other speakers at the symposium who focused on non-humans, Professors Fred Gould and Rodolphe Barrangou, come from North Carolina State University, as do others with this focus, such as Jennifer Kuzma and Todd Kuiken, among others. (It is probably not a coincidence but a fortunate causal event that this is where Dr. Enríquez got his Ph.D.)

[4] *See* HENRY T. GREELY, THE END OF SEX AND THE FUTURE OF HUMAN REPRODUCTION (2016).

[5] *See* HENRY T. GREELY, CRISPR PEOPLE: THE SCIENCE AND ETHICS OF EDITING HUMANS (2021).

proceed with genome editing in humans much more slowly and expensively than with non-humans. And our interventions on the 99.99999% of species that are *not* Homo sapiens may have extreme consequences with effects even on our own "divine" selves.[6]

Dr. Paul Enríquez's new book, *Rewriting Nature*, looks more at the effects of our biotechnologies on non-humans than either of mine.[7] And yet, in the time-honored tradition of people discussing someone else's book, after a few general comments on the book he wrote, I will talk mainly, and unfairly, of the book I wish he had written.

This is an ambitious and impressive book from a young, energetic scholar. It builds not just on his legal education, during and after law school, and his training in molecular and structural biochemistry, but on a series of four or five scholarly articles he has published since 2016. In it he thoroughly reviews genome editing—the science, its potential applications, and the policy and legal issues it raises. Chapter Five lays out a wide range of possible uses for genome editing, in humans first and then in non-humans.[8] Chapters Six and Seven focus on food;[9] Chapters Eight through Eleven, with the exception of the last nine pages of Chapter Eleven, are about genome editing in humans.[10]

I agree with many of Dr. Enríquez's positions on human germline genome editing, but I do think he makes an important error when he dismisses preimplantation genetic diagnosis ("PGD") as an alternative. He faults PGD for the "financial, medical, and emotional burdens; its low chance of success; and the large number of embryos that are discarded."[11] But these problems would be true for germline editing as well. It will necessarily require *in vitro* fertilization, which is the problem with PGD, and will almost certainly use PGD to see if the edited embryos carry the intended, and only the intended, changes.

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[6] The percentage is not made-up. There are thought to be about 8.7 million species of eukaryotic life on Earth, making Homo sapiens about one in 10 million. Camilo Mora, Derek P. Tittensor, Sina Adl, Alastair G. B. Simpson & Boris Worm, *How Many Species Are There on Earth and in the Ocean?*, 9 PLoS BIOLOGY 1 (2011),https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1001127 [https://perma.cc/92BT-A2JJ]. The estimate is quite uncertain, not least because of the problems of defining a "species." And it is an undercount as it makes only a very limited attempt to include number of species of bacteria and archaea, for which estimates range from a few thousand to, literally, trillions. *See* Stillianos Louca, Florent Mazel, Michael Doebeli & Laura Wegener Parfrey, *A Census-Based Estimate of Earth's Bacterial and Archaeal Diversity*, 17 PLoS BIOLOGY 1 (2019), https://doi.org/10.1371/journal.pbio.3000106 [https://perma.cc/RJ3D-82LR].

[7] *See* PAUL ENRÍQUEZ, REWRITING NATURE: THE FUTURE OF GENOME EDITING AND HOW TO BRIDGE THE GAP BETWEEN LAW AND SCIENCE 192-263 (2021).

[8] *Id.* at 141-68.

[9] *Id.* at 192-219, 244-55.

[10] *Id.* at 264-76, 287-312, 330-46, 360-71.

[11] *Id.* at 364.

Perhaps his most novel contributions are his idea of "jurisprudence of scientific empiricism"[12] and his proposed definition for "genome editing."[13] I would like to him flesh out the first approach more. It is described in the first chapter but makes only a few appearances in the rest of the book. On the second idea, definitions are tricky;[14] I worry about efforts to create a single definition, of genome editing or anything else, that fits all situations. And at least when the definition is to be used in regulation, it would probably make sense to allow the relevant agency to modify the definition, both to fit its applications today and to adjust to future changes in the technologies.

But let's talk about genome editing and non-humans, and what *I* wish Dr. Enríquez had written. First, I must praise him for devoting far more space to non-human genome editing than most authors do. I largely agree with the conclusions he reaches, but I wish he had pushed these issues farther in three ways: (1) more imagination, (2) a scope reaching beyond genome editing, and (3) more complete suggestions for a regulatory regime.

When Dr. Enríquez recounts in Chapter Five the possible uses of genome editing in non-humans, he touches on many topics: gene drives, invasive species, animals as research models, xenotransplants, crops, biofuels, and animal agriculture.[15] This is a fairly good list of economically or medically useful ways we could edit the genomes of non-humans. But it is not complete.

I wish he had stretched his imagination much farther. Other possible valuable uses include modifying organisms to help in cleaning up environmental problems through bioremediation and, perhaps, using them to concentrate economically valuable minerals. But the biggest thing missing from his list is the biggest problem in today's (and tomorrow's) world: climate change. Non-human genome editing clearly may (and I think will) play an important role in adapting to the changing climate, largely through modifying crops—it should prove easier to make corn more heat resistant than to move the corn belt 200 miles north—but also through, for example, adapting corals to higher ocean temperature and acidity.[16] More hopefully, it may prove possible to modify

[12] *Id.* at 10-15.

[13] *Id.* at 73-74.

[14] *See, e.g.*, Jacob S. Sherkow, Patricia J. Zettler & Henry T. Greely, *Is It "Gene Therapy"?*, 5 J.L. & BIOSCIENCES 786, 787-88 (2018) (exploring history and consequences of defining "gene therapy"); Henry T. Greely, *Banning "Human Cloning": A Study in the Difficulties of Defining Science*, 8 S. CAL. INTERDISC. L.J. 131, 131-32 (1998) (reviewing legislative and regulatory failures in defining "cloning").

[15] ENRÍQUEZ, *supra* note 7, at 145-159.

[16] *See* Phillip A. Cleves, Amanda I. Tinoco, Jacob Bradford, Dimitri Perrin, Line K. Bay & John R. Pringle, *Reduced Thermal Tolerance in a Coral Carrying CRISPR-Induced Mutations in the Gene for a Heat-Shock Transcription Factor*, 117 PROC. NAT'L ACAD. SCIS. 28899, 28899-900 (2020); Phillip A. Cleves, Marie E. Strader, Line K. Bay, John R. Pringle & Mikhail V. Matz, *CRISPR/Cas9-Mediated Genome Editing in a Reef-Building Coral*, 115 PROC. NAT'L ACAD. SCIS. 5235, 5235-36 (2018).

organisms so that they will pull greenhouse gases, notably carbon dioxide but possibly also methane, from the atmosphere and help sequester them.

Perhaps more importantly, the book ignores entirely the large amount of genomic editing we are likely to do to non-humans for largely non-useful ends.[17] We will modify our pets—we have already turned wolves into Shih Tzus and Great Danes; surely someone will make green poodles or glow-in-the-dark beagles.[18] We will transform our gardens. No one has been able to breed a truly blue rose; Clustered Regularly Interspaced Short Palindromic Repeats ("CRISPR") should make that feasible and perhaps easy. Someone will use various biotechnologies to create a unicorn or a (non-flying and miniature) dragon. Already people, organizations, and companies are working on "bringing back" extinct species, like the passenger pigeon or the wooly mammoth.[19] And at least some artists will have a field day, using living organisms as their materials. Scientists often feel constrained in what they do by the need to avoid a "wild" reputation in order get tenure, win grants, or be awarded prizes. Some artists, on the other hand, love notoriety; my own imagination is not sufficient to contemplate what they may do with genome editing, but, using "old fashioned" tools, "genetic art" is already several decades old.[20]

These may be viewed as frivolous uses of genome editing, but we are a frivolous species and will try many of them, and more. At least these uses are not intentionally evil. One must also note that CRISPR and other forms of genome editing of pathogens will likely make biological warfare easier against humans or, perhaps equally dangerous, against our crops and livestock.

Second, Dr. Enríquez makes some strong arguments for changes in our regulatory regime for genome-editing in humans but also in non-humans. The reasons for those changes, however, apply beyond genome editing as he defines it. His own book raises at least three kinds of modifications that I think are

[17] *See* R. Alta Charo & Henry T. Greely, *CRISPR Critters and CRISPR CRACKS*, 15 AM. J. BIOETHICS 11, 11-13 (2015).

[18] For example, Chinese researchers used genome editing to make highly muscled beagles seven years ago. Antonio Regalado, *First Gene-Edited Dogs Reported in China*, MIT TECH. REV. (Oct. 19, 2015), https://www.technologyreview.com/2015/10/19/165740/first-gene-edited-dogs-reported-in-china/ [https://perma.cc/W2W4-MHNK].

[19] *See* Jacob S. Sherkow & Henry T. Greely, *What If Extinction Is Not Forever?*, 340 SCIENCE 32, 32-33 (2013); REVIVE & RESTORE, https://reviverestore.org (last visited Jan. 23, 2022) (non-profit organization dedicated to using biotechnologies to preserve and strengthen endangered species and to revive extinct ones); COLOSSAL LAB'YS & BIOSCIENCES, https://colossal.com (last visited Jan. 23, 2022) (working on practical, working model of de-extinction); Matthew Herper & Megan Molteni, *Return of the Mammoth? George Church-Backed Company Launches with $15 Million for Elephant-Sized Quest*, STAT NEWS (Sept. 13, 2021), https://www.statnews.com/2021/09/13/woolly-mammoths-george-church-colossal-launches/ [https://perma.cc/AL99-3KSR].

[20] For a gorgeous book that includes both discussion of genetics and art inspired by it, see IMAGINING SCIENCE: ART, SCIENCE, AND SOCIAL CHANGE (Sean Caulfield & Timothy Caulfield eds., 2008).

beyond his definition: non-targeted DNA modifications, cloning, and epigenetic modifications. If these can have similar consequences to genome editing, should not their regulation also be revisited?

Biotechnologies beyond directly modifying DNA or its expression present the same question. We will be able to change organisms markedly through, among other things, making new kinds of hybrids (crosses between species that might not be able to interbreed naturally) or chimeras (organisms with DNA from two or more different individuals, sometimes from very different species).[21]

We are likely even to probe the borders of "living" organisms. One course would be to give non-human animals "prostheses," making them non-human "cyborgs." (Researchers have already created rats with brain implants that allow them to be, somewhat, controlled.[22]) Another could be to create "things" that are designed from the bottom up to be part organism and part machine. One example of such a "biobot" is a small, hinged disk that has, on one side, rat heart muscle cells modified to contract when illuminated with light of a particular frequency. Shine the light, they contract and the two sides of the hinge close; stop the light, they relax, and the disk reopens.[23]

Dr. Enríquez's concerns, like mine, include animal welfare, environmental risks, and negative public reactions. Genome editing can raise those issues, but so can other ways we will modify life. Why not think about broader policy responses and regulatory regimes that deal with more of the problems than those caused by genomic engineering?

Finally, the policy and regulatory changes Dr. Enríquez recommends seem, to me, too weak. The book's discussion of regulation of non-human genome editing looks exclusively at crops, and mainly crops that are eaten rather than used for fiber or other material, such as cotton or timber. It offers some good ideas for building public confidence in these new products and on how to use "omics" to establish substantial equivalence.[24] But his basic position is that if no meaningful differences exist between non-regulated and regulated crops, neither should be regulated. Of course, that is not the only possible answer—one could

[21] If, as I believe, we will soon to be able to make functional eggs and sperm from skin cells in humans and other species, as has already been done in mice, see GREELY, *supra* note 4, at 102, we could create, within or perhaps between species, individuals with far more than two parents as a "non-genome editing" way of changing DNA. *See* Sonia M. Suter, *In Vitro Gametogenesis: Just Another Way to Have a Baby?*, 3 J.L. & BIOSCIENCES 87, 87 (2015).

[22] This work goes back 20 years. *See* Sanjiv K. Talwar, Shaohua Xu, Emerson S. Hawley, Shennan A. Weiss, Karen A. Moxon & John K. Chapin, *Rat Navigation Guided by Remote Control*, 417 NATURE 37, 37-38 (2002); Guy Gugliotta, *Rats Turned into Remote-Controlled Robots*, WASH. POST (May 2, 2002), https://www.washingtonpost.com/archive/politics/2002/05/02/rats-turned-into-remote-controlled-robots/e7db8baa-c49a-4aef-8bbd-4144e0d32105/.

[23] Sung-Jin Park, Mattia Gazzola, Kyung Soo Park, Shirley Park, Valentina Di Santo, et al., *Phototactic Guidance of a Tissue-Engineered Soft-Robotic Ray*, 353 SCIENCE 158 (2016); *see also* Steph Yin, *Stingray Robot Powered by Light, and Living Rat Cells*, N.Y. TIMES (July 11, 2016), https://www.nytimes.com/2016/07/12/science/stingray-robot.html.

[24] ENRÍQUEZ, *supra* note 7, at 371-78.

regulate both (and, as argued above, not just for genomic editing but for many biotech interventions in non-human organisms).

My current thinking would have a significant regulatory scheme but one that would vary with the degree of risk involved. All those attempting these changes would be required to register their intent with some designated authority (maybe a government agency, maybe a private organization). The researchers would have to provide information on what they are trying to do. Where the risk warrants it, the relevant authority may require health or environmental testing of differing stringency. (The idea of using various omics methods for this testing is an excellent one.) Different rules will apply to organisms confined to laboratories or other restricted habitats compared with those to be released into the environment. Researchers would have to "sign" their, or their institution's, identity into the organisms' DNA. And they would have to a plan for reasonable ways to clean up any messes if things go wrong. Methods could include everything from biological "kill switches" to insurance policies. I may modify this broad outline at some point and, of course, my approach may be, in a wide range of ways, wrong—but I am confident that some significant regulation will be needed for both genuine safety reasons and to bolster public confidence and, hence, acceptance, of the work.

Rewriting Nature is exciting. It is exciting for its coverage and its ideas, and it is exciting as the announcement of an interesting new player in the world of genomics policy. I look forward to reading much more from Dr. Paul Enríquez—especially if it is about non-human organisms!