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ARTICLES

In Humans, Sex is Binary and Immutable

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This article says nothing novel. It discusses a fact as well-established as the billions of years of evolution that shaped our species. We live in a world, however, that increasingly ignores such truths, and in which the combination of awareness and courage to set the record straight appears rare.

A disclaimer: I am not a tenured faculty member and have no job security; I am well aware that my career prospects could be jeopardized by this essay. I also write from a perspective—not widely shared—that anyone who pledges allegiance to any political party or ideology cannot rightly call himself a scientist. Political and ideological loyalties, in my view, violate the epistemic practices scientists are supposed to follow.

Denying the Sex Binary

In late 2018, the current U.S. presidential administration circulated a memo directing government agencies to adopt a definition of gender "determined by the genitals that a person is born with."[1] Much outrage followed, even including protest rallies at prestigious medical schools. More than 2,600 scientists signed a statement claiming that "[t]here are no genetic tests that can unambiguously determine gender, or even sex."[2] *Nature*, the world's premier science journal, ran an editorial stating that "the research and medical community now sees sex

[1]Erica L. Green, Katie Benner, Robert Pear, " 'Transgender' Could Be Defined Out of Existence Under Trump Administration," *New York Times,* October 21, 2018.

[2]Transgender, Intersex, and Gender Non-Conforming People #WontBeErased by Pseudoscience, October 26, 2018, https://not-binary.org/statement/

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as more complex than male and female"' and "the idea that science can make definitive conclusions about a person's sex or gender is fundamentally flawed."[3]

These are remarkable statements as they are equivalent to outright denial of humans' biological nature. Numerous publications promoted such positions. *Nature* had previously published an editorial titled "Sex Redefined," boldly stating that "[t]he idea of two sexes is simplistic. Biologists now think there is a wider spectrum than that."[4] Popular science magazines such as *Scientific American* and *National Geographic* told readers that "the science is clear and conclusive: sex is not binary,"[5] a view even more aggressively pushed in mainstream media, where we regularly read that "biologists now think the idea of two sexes is inaccurate."[6]

Much has been written by feminist authors about the non-binary nature of "gender," where "gender" is defined as something "socially constructed," distinct from sex. But biological sex itself is also under attack. Feminist philosophers such as Judith Butler and Anne Fausto-Sterling initially advanced the view that both gender and sex are "socially constructed," denying the objective reality of binary biological sex, and academic writings promoting this view continue to be produced.[7]

Usually this is done by taking a list of criteria for dividing humans into two sexes—anatomical/gonadal/hormonal/chromosomal/genetic/genomic/brain/neural sex—and matching that list to examples of "intersex" conditions not fitting neatly on either side, supposedly discrediting the binary. But the topics that truly matter for understanding sex—gametes, reproduction, and evolutionary selection pressures—are missing from such treatments.

Yet this has become mainstream, and an unquestionable dogma too, even within the hard sciences. This is disastrous, as the objective truth is that sex in humans is strictly binary and immutable, for fundamental reasons that are common knowledge to all biologists taking the findings of their discipline seriously. Denying that sex in humans is binary attacks the very foundations of the biological sciences. This needs to be properly summarized and openly articulated.

[3]"US proposal for defining gender has no basis in science," *Nature* 563 (2018):5

[4]Claire Ainsworth, "Sex redefined," *Nature* 518 (2015):288—291.

[5]Robin M. Henig, "How science is helping us understand gender," *National Geographic,* January 2017; The Editors, "The New Science of Sex and Gender," *Scientific American*, September 1, 2017.

[6]Anne Fausto-Sterling , "Why Sex Is Not Binary," *The New York Times*, October 25, 2018.

[7]V. Sanz, "No Way Out of the Binary: A Critical History of the Scientific Production of Sex," *Signs: Journal of Women in Culture and Society* 43 (2017):1-27

The Nature of Self-replicators and Organisms

To understand the nature of human sex, we need to review our place in the grander scheme of life on Earth. We do not know exactly how life appeared on our planet but we do know some of the features it had from the beginning. Key among these is the self-replicating nature of genetic material and its relationship to the organism. Because of our anthropocentric bias, we tend to see genes as existing with the "purpose" of encoding for the organism. However, to the extent we can speak of "purpose" in biology, the relationship is exactly the opposite—the organism exists to propagate its genetic material, and this is the sole "meaning" of its existence.[8] Getting that relationship backwards is the ultimate cause of most falsehoods propagated in the debates around gender and sex.

There are two broad hypotheses regarding life's origins, usually shortened as "metabolism-first"' and "genetics/replicators-first." Both hypotheses converge onto a state, in which evolution is Darwinian (i.e. descent with modifications of genetic material), and life is one unbroken succession of self-replicators making more copies of themselves. Cells (and complex multicellular organisms) can be seen as being put together around self-replicators to facilitate the process. This realization mandates a radical rethinking of who and what we are. This understanding, however, has not yet spread very far into public consciousness because much of what makes it obvious and uncontroversial has been learned only in the last few decades.

One such important piece of the puzzle is the nature of prokaryote genomes. The concept of "species" was developed based on observing and studying multicellular organisms and does not really make sense for prokaryotes. By force of habit, "species" were traditionally assigned to bacterial strains, and it was assumed that each such strain had a "genome." But once multiple genomes were sequenced for different strains, a striking discovery emerged—there was no such thing as a specie's genome. Instead, each strain contains a relatively small number of common genes, together with some small portion of a larger set belonging to a "pan-genome."[9] Genes in the pan-genome are exchanged, often quite rapidly, through various mechanisms for horizontal gene transfer (HGT).

Such discoveries dramatically shift our focus towards a gene-centric view of evolution—genes are exchanged, creating new combinations and phenotypes,

[8]Richard Dawkins, *The Selfish Gene* (New York: Oxford University Press, 1976).

[9]H. Tettelin, V. Masignani, M.J. Cieslewicz et al., "Genome analysis of multiple pathogenic isolates of *Streptococcus agalactiae*: implications for the microbial 'pan-genome'," *Proc Natl Acad Sci U.S.A.* 102 (2005):13950-13955.

on which natural selection acts, determining how successful the propagation of those genes is, with the individual cells being rather ephemeral temporary entities.

Mobile genetic elements (MGEs) and viruses take that principle to the extreme—if gene propagation is the primary evolutionary objective, there is no requirement for any "progress" towards more "complex" entities. There can just as well be no organism involved as long as genetic material is replicated. This is the strategy adopted by viruses (only "alive" when inside a cell they have hijacked) and MGEs (not even encoding for viral particles, their sole capacity being ensuring their replication).

What sex is and how and why it evolved can only be properly understood in this context.

Why There is Sex

There are two types of cellular life on Earth: prokaryotes and eukaryotes. Prokaryotes have a simple organization, usually lacking the hallmark features of eukaryotes, such as nucleus, endomembrane systems, mitochondria, etc. Life is also divided into two lineages, not coinciding with the prokaryote/eukaryote divide. Prokaryotes are split into bacteria and archaea, with eukaryotes evolving as a result of a fusion between an archaeal host and a bacterial endosymbiont.[10]

The subsequent complexification of eukaryotes gave rise to their modern features, one of them being meiosis (reductive cell division creating haploid cells/gametes) and sexual reproduction. Prokaryotes reproduce asexually and lack meiosis. They do, however, employ mechanisms for exchanging genetic material, which they do on a massive scale.[11]

The ubiquity of genetic material exchange mechanisms strongly suggests that recombination is advantageous. Although it is not possible to concisely summarize the vast literature on the subject,[12] we will focus on just a few crucial points.

The first key concept is evolutionary fitness. Fitness is most often expressed as a selection coefficient s, which ranges from -1 to infinity, where $s = -1$ corresponds to lethality/complete sterility.

[10]E.V. Koonin, "The origin and early evolution of eukaryotes in the light of phylogenomics," *Genome Biol* 11 (2010): 209.

[11]P. Puigbo, Y.I. Wolf, E.V. Koonin, "The tree and net components of prokaryote evolution," *Genome Biol Evol* 2 (2010):745–756.

[12]N.H. Barton, "Why sex and recombination?," *Cold Spring Harb Symp Quant Biol* 74 (2009):187–195.

Sexual reproduction is costly to an individual as it involves producing gametes, yet only half of one's genes are transmitted to the next generation. The classical argument for why there is sex is that it helps create new favorable combinations of alleles.[13] However, just as it can create favorable combinations, recombination can also break up existing ones. Asexually reproducing organisms would naively be expected to have an advantage. So why have sex?

The "Fundamental Theorem of Natural Selection"[14] states that the increase in mean fitness due to natural selection equals the additive genetic variance in fitness. In real organisms, different loci are physically linked in various ways; fitness is therefore affected by the associations of alleles with each other. If negative such associations (i.e. between beneficial and maladaptive alleles) predominate, recombination will act to increase variance in fitness; mechanisms for recombination will thus be selected through their association with generating favorable variation and the overall higher fitness of the recombining genotypes.

An additional consideration is that real-life populations are finite and stochastic fluctuations of allelic frequencies ("genetic drift") play a major role. Without recombination, genetic drift and linkage disequilibrium together lead to linked loci interfering with each other's response to selection.

Absence of recombination is predicted to result in irreversible accumulation of deleterious mutations ("Muller's ratchet"). This is indeed what is observed. Obligate asexuals arise occasionally among eukaryotes, but they tend to go extinct quickly. The one notable exception are bdelloid rotifers, which have been asexual for around 70 million years. However, this is an exception proving the rule, as it appears that HGT (otherwise rare in eukaryotes) plays the role of recombination in these animals.[15]

Bdelloids and prokaryotes illustrate an important point: meiosis and recombination are not the same thing. Recombination can be accomplished through a variety of mechanisms. In eukaryotes that mechanism is meiosis. Why exactly it evolved in its current form is not clear. Eukaryotes cannot exchange DNA freely the way prokaryotes do, because of the presence of the nucleus and the physical organization of their chromatin. Some alternative was needed, but we cannot be certain whether meiosis was the only possible

[13] A. Weismann, "The significance of sexual reproduction in the theory of natural selection," in *Essays upon heredity and kindred biological problems,* ed. E.B. Poulton, S. Schonland, A.E. Shipley (Oxford: Clarendon, 1889), 251—332.

[14] Ronald A. Fisher, *The Genetical Theory of Natural Selection* (Oxford: Clarendon, 1930).

[15] J. Felsenstein, "The evolutionary advantage of recombination," *Genetics* 78 (1974):737—756; H.J. Muller, "Some genetic aspects of sex," *Am Nat* 66, no. 703 (1932):118-138; N.A. Moran, "Accelerated evolution and Muller's rachet in endosymbiotic bacteria," *Proc Natl Acad Sci U S A* 93 (1996):2873—2878.

solution. In any case, evolve it did, and very early in eukaryote evolution too, prior to the Last Eukaryotic Common Ancestor (LECA).[16]

Sex Determination and Mating Systems

Eukaryotes are immensely diverse, and exhibit much variation in sexual reproduction mechanisms and life cycles. But two variables are key: the alternation of generations and the size of gametes. The eukaryote life cycle follows a general pattern of alternating haploid (1*n* set of chromosomes) and diploid (2*n*) generations. Diploid cells can undergo meiotic divisions, producing haploid cells, while haploid cells can fuse into a diploid cell. Whether haploid and diploid cells undergo nonreductive mitotic divisions determines the type of life cycle. Animals are diplontic (only diploid cells divide). Most fungi are haplontic (only haploid cells do), land plants are haplodiplontic (both generations divide), algae and protozoans exhibit a wide diversity of life cycles.

There are also three types of fertilization: isogamy, anisogamy and oogamy. Isogamy features morphologically similar gametes, and is common in unicellular eukaryotes. Almost certainly it was the ancestral LECA condition.

On multiple occasions, isogamy evolved into anisogamy, i.e. production of two different gametes. In some lineages, anisogamy further evolved into oogamy, the classic example being practiced by animals. By convention, larger gametes are taken to be the egg/"female" while smaller gametes are the sperm/"male." Why has anisogamy evolved? The traditional model proposes that eggs will become bigger if fitness increases non-linearly with increased egg size. Although a rather unusual assumption, it does appear to hold in multicellular organisms.[17]

Several important points follow:

1. Meiosis and gamete fusion evolved to allow for recombination to happen; once they came to exist, generations must inevitably alternate. The organismal complexity of the two generations can be immense, but it is of little importance for what is actually happening—haploid gametes fuse to form a diploid cell, from which, or from its lineage, haploid gametes have to then again be produced to restart the cycle. Overt focus on human-specific complexities often obscures these deeper underlying processes.

[16]D. Speijer, J. Lukes, M. Elias, "Sex is a ubiquitous, ancient, and inherent attribute of eukaryotic life," *Proc Natl Acad Sci U S A* 112 (2015):8827–8834.

[17]E.R. Hanschen, M.D. Herron, J.J. Wiens et al., "Multicellularity Drives the Evolution of Sexual Traits," *Am Nat* 192 (2018):E93–E105.

2. At the level of gametes, sex in eukaryotes is inherently digital—two gametes fuse together to form one zygote. Yet it need not be binary—more than two mating types can exist,. Indeed, this is what many unicellular eukaryotes practice (some can have >100 mating types.)[18] However, "non-binary" sex does not mean "non-digital" sex. Mating types are distinct and finite in number, with no continuum between them, and they mate pairwise.
3. Having more than two mating types is restricted to isogamous lineages. Anisogamy is inherently binary, and the fusion of one of each gamete type is necessary for reproduction.
4. The type of gametes produced is a very objective criterion for classifying the sex of an individual, and is its fundamental defining feature. In metazoans, there are only two types of gametes, although they do exhibit enormous diversity in the relationship between the individual and gamete production and fertilization. Numerous species practice parthenogenesis, many are predominantly hermaphroditic (e.g. earthworms and snails), while individuals of some species can change their sex (e.g. clownfish).

However, no such examples have ever been observed in mammals, in which binary sexual reproduction appears to be extremely strongly enforced.

Why is that? Genetic imprinting is the most likely answer. A subset of genes are only expressed from either the parental or maternal chromosome, with DNA methylation controlling the pattern. Why imprinting evolved in mammals is another evolutionary puzzle;[19] for our purposes its existence is of primary importance.

That both a male and a female gamete contribute to the zygote is vitally necessary–debilitating human diseases result from disturbing the imprinting of even single genes (Prader-Willi syndrome, Angelman syndrome, etc.). Yet 100 or more genes are imprinted in total. Disrupting imprinting for all of them is incompatible with life. This explains why the male-female binary at the organismal level is so tightly locked in place in mammals.

Admittedly, imprinting explains why there is no parthenogenesis, but does not fully explain why there are no true hermaphrodites (i.e. individuals producing both sperm and eggs). This is inherently near-impossible because in mammals the two gonads inhibit each other's embryonic development (e.g. the Anti-Mullerian Hormone inhibits the development of the female reproductive system in males).

[18]S.S. Phadke, R.A. Zufall, "Rapid diversification of mating systems in ciliates," *Biol J Linnean Society* 98 (2009):187-197.

[19]T. Moore, D. Haig, "Genomic imprinting in mammalian development: a parental tug-of-war," *Trends Genet* 7 (1991):45–49.

Why "Intersex" Conditions Do Not Invalidate the Sex Binary

But what about "intersex" individuals? Unfortunately, confusion and misunderstanding reign when it comes to their existence. Humans are indeed born with a variety of "intersex" conditions at low frequency, but that does not mean that these conditions are part of normal healthy variation. Humans are also born with a great variety of devastating congenital deformities and diseases, and if alien exozoologists were to write a description of *Homo sapiens* based on extensive observations of the population, such a description would never feature, for example, anencephaly, and neither would it include anything else but binary sex.

Extremely deleterious phenotypes, especially when their fitness is invariant with respect to environmental conditions, cannot be part of that description, as they are by definition actively eliminated from the population. The mathematics of natural selection is remorseless. For the human population, even an allele with an initial frequency as low as 0.01 and selection coefficient s = 0.05 is nearly ensured fixation. On the other hand, that should not be taken to mean that natural selection is all powerful. First, even if an allele is strongly deleterious, its frequency will not be zero, as it is constantly reintroduced by mutations at some rate μ. Second, alleles with small selective (dis)advantages are not ensured fixation. Genetic drift can lead to fixation of alleles with small selective coefficients irrespective of their effects, as long as $s < \sim 1/N_e$ (N_e is the effective population size).

Therefore we cannot expect "perfection" from biological processes. Imagine that a biochemical reaction runs with a given accuracy in a finite population. The selective advantage of mutations improving its accuracy will generally be at most the fractional improvement that they confer. Thus it is not possible for selection to push the system towards absolute perfection as further fractional improvements are "invisible" to it if smaller than the selection barrier $\sim 1/N_e$. Errors are thus expected to occur everywhere, and indeed they do. This is why important genes get mutated, developmental processes get disrupted, and the results are newborns with very low fitness.

These facts bear on how we are to think about "intersex"' people. The great diversity of such conditions cannot be explored here in detail. These include Androgen Insensitivity Syndrome (feminization of males due to androgen receptor mutations), Klinefelter's syndrome (47,XXY karyotype), XX male syndrome (46, XX "males" due to translocation of the master regulator *SRY* to the X), Turner's syndrome (45,X0) and many others.

These conditions present with a variety of phenotypes intermediate between typical male and female features, but they have one crucial

commonality—individuals afflicted are almost invariably sterile.[20] On the few occasions where fertility is possible, the phenotypes are mild and it is hard to even call them "intersex." Their evolutionary fitness is therefore as negative as fitness could possibly be short of being stillborn (s = -1 for sterile individuals). Importantly, these fitness reductions are invariant to environmental variables. It is possible for a condition that is a debilitating disease under some circumstances to be beneficial under others (e.g. sickle-cell anemia and malaria). But this does not apply to the inability to produce viable gametes, which makes one unable to reproduce under all circumstances.

All "intersex" conditions, when examined, clearly arise from single-gene mutations or chromosomal aberrations on a genetic background that would have indisputably been producing male or female gametes had these mutations not occurred, and, rarely, due to chimerism (i.e. individuals made up of both male and female cells). True hermaphrodites possessing both sets of functional gonads and genitalia have never been observed in *Homo sapiens*.

Therefore the "intersex" argument against the sex binary is simply not valid. Intersex individuals exist only because of continuous *de novo* reintroduction of the relevant mutations in the population, recessive genes becoming unmasked, or disruptions of normal embryonic development.

Sex in mammals is on a fundamental level binary and immutable, and claims that "intersex"' individuals disprove that can only be made in the absence of any consideration of the biological nature of humans and how our evolutionary history has shaped our biology. Which brings us to the most worrying aspect of the widespread adoption of such denial.

The Coming Battle

The reasoning outlined above rests on two assumptions. First, population genetics is true, and second, common descent from the original self-replicators is true. That "population genetics is true" means that our knowledge of inheritance mechanisms is broadly correct, i.e. we understand molecular biology sufficiently well, and "random" events (mutations and gamete segregation) are truly random, i.e. they happen with no foreknowledge of their future consequences.

If these assumptions are accepted, what I have argued here regarding the binary nature of biological sex in humans is incontrovertibly true. It follows directly from the basic relationship between genes, organisms, recombination,

[20]J.P. Van Batavia, T.F. Kolon, "Fertility in disorders of sex development: A review," *J Pediatr Urol* 12 (2016):418-425.

and reproduction. If mutations are random and undirected, then genetic material is the key entity in the center of the evolutionary process, not organisms. The inverse is also true—if the binary nature of biological sex in humans is to be denied, that automatically requires the rejection of one or both of these assumptions, for otherwise the binary nature of sex cannot be denied.

As these assumptions are foundational for modern science, a troubling realization follows—a direct attack against the hard sciences can be expected from the people who deny the binary nature of human sex. So far it has not happened, but there have been warning signs and it might just be a matter of time and of little understanding of the deep philosophical contradictions involved.

Certain parallels can perhaps be made with battles over the teaching of evolution, but there is one critical difference—the ideas in question here are coming directly from within the highest ranks of academia, where they appear to have significant institutional support, and, as recent years have demonstrated, their proponents are more than willing to use aggressive tactics outside the scholarly realm to silence their critics. There is also little understanding of the seriousness of the situation within the scientific community, which, whether for political reasons or due to lack of awareness, has been willingly supporting outright "bio-denialism."

I hope that this text will help prevent the potential damage by providing the plain statement of the fundamental biological facts that, until now, did not exist, and that it will serve as the foundation for pushing back against the insanity.