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Clarissa's House

A famous literary heroine did herself in for no good reason, but life is doing that all the time for all the right reasons

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The longest novel in European literature is said to be *Clarissa, or the History of a Young Lady*, a 1,500-page (small print) giant published in 1748 by Samuel Richardson (Fig. 1). *Clarissa* was a runaway best-seller and has remained in print ever since. It is a great novel for a patient or obsessive person who wants the satisfaction of endurance or of nostalgically recapturing the slower pace of long evenings lit by whale-oil lamps. *Clarissa* was also one of the first epistolary novels, in which the players tell their stories exclusively through exchanges of letters.

Clarissa was an 18-year-old ingénue, daughter of the country gentry. Pressured by her family's greed for wealth to wed a man she found obnoxious, she was lured away by a notorious libertine whom she fancied was just helping her to escape. Intrigued by him, but also trying to retain an over-starched morality, she resisted his increasingly warm advances. He spirited her away from her overbearing family and installed her in residence upstairs of a gentile London brothel he had frequented. Eventually, after a long period of threats and persuasion, he drugged and violated her.

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Nobody believed Clarissa's claims of innocence. Expressed in a stream of plaintive letters, Clarissa, feeling moral humiliation, wished herself to waste away. In a rather melodramatic gesture, she told friends she would use her remaining resources for a single purchase, a house to which she could escape the shame of her London entrapment. They liked the idea until they were stunned to discover it was more drama than domicile, because the "house" Clarissa bought was a coffin (Fig. 2), which she insisted be kept in her sickroom to await her final "moving" day. In the end, Clarissa died, moved into her house, and through belated forgiveness was allowed to be buried in the family plot. As for Lovelace, the libertine who had violated her honor, he was soon killed in a duel with Clarissa's cousin, who had been one of her few allies.

Clarissa's house represents a needless death wish, the fancy for release to a better world and redress for inadvertent wrongs. To a biologist, a suicide or any other form of self-limitation seems not just needless, but downright hard to explain because survival is the fittest of mandates. Evolution cannot favor genes that disfavor themselves.

Readers who are old enough may remember that in the 1970s explaining selfless behavior in evolutionary terms was a mainstream research topic in biology and anthropology. Many of the issues related to Thomas Malthus' ideas about overpopulation, which had been so important to the development of the theory of natural selection by Darwin and Wallace. Malthus suggested that one response to the ubiquitous challenge of population pressure was to reduce fertility. Field biologists, animal behaviorists, ethologists, and anthropologists gathered worldwide data on fertility-reduction mechanisms such as delayed marriage, homosexuality, infanticide, abstinence, high bride-price, prescriptive marriage that left few eligible mates in aboriginal societies, lactational infertility, and others. Malthus was a social thinker, but a biologist wonders how individuals could be induced to undergo such self-restraint.

Sparks flew in 1962 when V. C. Wynne-Edwards[1] published a Darwin-scale and rather Darwin-imitative volume arguing that self-imposed population-based fertility restraint by various means was widespread in the animal world, forms of group selection that obviated the single-minded Darwinian focus on individual competition. Classic responses included G. C. Williams' book[2] vigorously defending the Darwinian orthodoxy that selection could only work for the good of a selfish gene or at least an individual, not a group. Fertility control or other forms of social altruism worked only if they enhanced the chances of at least some offspring by reducing the number of competitors for family resources.

A general evolutionary explanation for self-sacrifice was formalized by W. D. Hamilton's[3] idea of kin selection or inclusive fitness, that self-repression can evolve if the altruist adds more fitness by the act than the inverse of the kinship relationship to the beneficiary: to help your sibling have at least two additional children, you can give up one of your own.

Figure 1. Samuel Richardson (1689–1761). Source: public domain.

Related ideas, like reciprocal self-restraint, were also proposed to explain away even the *appearance* of group selection.[4] E. O. Wilson's *Sociobiology*[5] gave a name to this world-view in which nothing succeeds like the individual's own success.

Sociobiology is about the special cases of social organisms acting in what, on the surface, may appear as being only for the good of the group. By now, everyone knows about the birds (their decoying calls) and the bees (their sterile workers), but there's a lot more to life than mock and honey. Self-restricting deeds are not restricted to social organisms, human or otherwise. They also are not an exception that needs special theoretical pleading. Instead, self-restraint is taking place all the time and at all levels of life. It is more the rule than the exception.

APOPTOSIS: DEATH BY CHOICE

It has long been known that during embryonic development various kinds of cells die in systematic ways that are consistently observed among embryos within and even among species. The organization of the brain occurs by this kind of cell death, when neurons are guided into position as they migrate through various layers of the developing brain. Likewise, the branching of organs like salivary glands, toes, and fingers is sculpted by cell death. An overall mold of the structure, like a foot pad, is first formed; then, as the condensations for future toe-bones form, the cells in between the digits die (in species without webbed feet).

In 1972, this phenomenon was named *apoptosis* (pronouncing the second "p" is optional).[6] Apoptosis is also known as programmed cell death because it has been shown to have an active, elaborate, evolutionarily ancient genetic basis. Cells in developmentally specific places in embryos have receptors on their surface that detect external signal molecules; these molecules activate cascades of genetic activity within the cell, causing the nucleus to crumble and the cell's innards to form small fragments called apoptotic bodies. The cell breaks apart, after which patrolling white blood cells called macrophages come along and scavenge the fragments. The process involves many different actively enabled mechanisms employing large numbers of different genes. (Diagrams of these genetic pathways are readily available on the web by key-wording "apoptosis.")

An embryo is a vibrant creative testament to a future. But it and, indeed, your body as you read these lines, are also abattoirs, housing swathes of cellular slaughter. It's estimated that an adult human ushers out billions of its own cells in this way every day as part of normal tissue renewal. Interesting as that is, however, apoptosis is by no means the only example of self-restraint within an organism. There are many others. They go below the level of cells, and they're happening all the time. Without them, you would not be you.

MAMA SAYS IF YOU CAN'T EXPRESS SOMETHING GOOD, EXPRESS NOTHING AT ALL

Even within healthy cells, from a genetic point of view, most of what you do in life is what you *don't* do. The human genome encodes roughly 20–25,000 different protein-coding regions (traditional genes) as well as many other genetic functions. But in a given type of cell, most genes are *not* expressed. They are not used by the cell; they are quiescent. This self-restraint is one of the most characteristic aspects of genes. In fact, the function of many if not most of our genes is to regulate the expression of other genes, including themselves.[7]

Chromosomes are gigantically long DNA molecules compactly packaged inside the nucleus. The DNA is coiled around spool-like proteins called histones that attach at roughly regular intervals, their position depending in part on the sequence itself. This packaging makes genes inaccessible to the expression-inducing machinery. Hence, those genes are silently wrapped in a temporary coffin with the lid closed. The genes must feel very frustrated, huddled masses selfishly yearning to breathe free. And then, in specific contexts they do: the

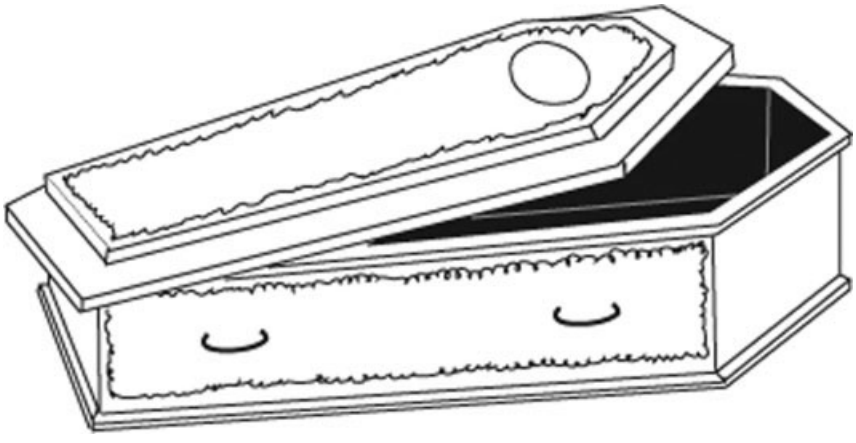

Figure 2. Clarissa's house. Source: Drawing by Anne Buchanan.

histones that cover their chromosome region are chemically modified by a process called acetylation, which loosens the coiling. This loosening allows access to the DNA by proteins needed for the gene to come, like a vampire at midnight, out of its coffin, back to life, to be transcribed into RNA such as the messenger RNA that is, in turn, translated into protein.

But histone modification is not the only way a gene is repressed. Even within unwrapped DNA, not all genes are liberated. Which ones are depends on a second kind of chemical change. The DNA near a gene can be methylated, modified by what amounts to chemical bristles that keep the transcription proteins at bay, preventing the gene from being expressed. But when the gene is needed, the methylation is stripped away. Like acetylation, methylation and its removal are done by ancient, active mechanisms.

A different kind of genetic restraint has recently been discovered to have much broader use than had been suspected. As diploids, we have two copies of each chromosome. It was long thought that when a gene is needed, both copies are used, but in 1961 Mary Lyon discovered that in females one of the two X chromosomes is inactivated; the cell uses only the genes on the active copy.[8] The random choice of which X to use is made early in embryonic development. Once made, however, the descendants of each cell keep using the chosen copy. As a result, some patches of females' cells use the paternal X, others the maternal, making every woman a uniquely mosaic exemplar of genetic restraint.

Surprisingly, this is not the only instance of gene exclusion. Many other areas in the genome—some estimate that there are around 1,000 of them—also express only one of their cell's two existing copies. Many genes are "imprinted" by methylation, sometimes in the sperm or egg cell before fertilization, so that only one of the two copies in the embryo is expressed. The choice is again random and early, and remembered by descendant cells. Odorant receptors, color vision, and immune system genes are examples. Also, it is not just one of the two chromosome copies that is repressed. These genes are arranged on their respective chromosomes in tandem arrays of similar, evolutionarily related genes. But in addition to the fact that only one of the two chromosomal copies is active, only one of the string of related genes is active, also randomly picked, while its closely related kin on the same chromosome are not active.

Figure 3. Norns weaving the fate of the world. Nineteenth-century drawing by Arthur Rackham for Wagner's *Ring of the Niebelungs* operas.

Whole classes of entirely different, also ancient mechanisms that quickly inhibit gene expression have recently been discovered.[9] They involve DNA that is transcribed into various types of RNA that act directly rather than being translated into protein.[10] One representative is RNA interference (RNAi). In RNAi, noncoding RNAs are produced. These RNAs have short sequence elements complementary to specific messenger RNAs. They recognize and bind tightly to that mRNA in a death grip that exposes the latter to destruction, dashing its dream of being translated into protein. By RNAi, the cell maintains tight restraint on the self-interested impulses of its own genes.

EVOLUTIONARY FATE THAT IS PREDICTABLE

The plethora of means by which cells and genes are inhibited has proliferated over eons of time. It is interesting to speculate about their evolutionary origins. Two facts seem relevant. The venerable age of the mechanisms suggest that they may have existed in the ancient unicellular world. For example, RNAi may have first been used by microorganisms as a defense against parasites to grab and chop the RNA of infecting viruses. The second fact is that not even microorganisms are a Babel of uncontrolled gene expression. They use their genomic repertoire differently according to circumstance. Perhaps long ago the price cells paid for a babbling chaos of gene expression was doom. That may have enabled multicellular organisms, with disciplined cells that did different things in different tissues, to arise in the first place.

A key aspect of Darwinian theory is that evolution is not predictable. Chance, or drift and various kinds of selection sort the future from the array of what happens to be present today. This is a critical difference from Lamarckian evolution in which organisms strive to become something they're not, but can yearn for. Genomes today don't contain the genomes of future generations.

Development is also a form of evolution, but among cells and with its own characteristics.[11,12] Like the Norns weaving the thread of each person's fate in Norse mythology (Fig. 3), the future of a single fertilized egg cell as it diverges into an ecology of cytospecies is predictable and replicable: the embryo is composed of tissues in which cells have different characteristics, functionally distinct and isolated from each other. Unlike the chance nature of genetic drift on the evolutionary scale, it's not just chance that determines which cells shall live and which shall die, which genes shall be expressed and which repressed. Instead, it's highly predictable; as the genome "unravels" to weave the embryo, the fate of some cells in specific contexts is to be induced by their genomically identical twin cells to do the suicidal deed.

From a Darwinian evolutionary viewpoint, it's tempting to view a cell's voluntary self-repression as inclusive fitness *in extremis*, because its self-control helps billions of copies of the suicide's same genome in the other cells in the organism, whereas the fated cell by itself could only divide and produce two daughter cells. From that perspective, cells should stampede like lemmings for self-sacrifice.

But this is misleading, because for cells and genes this isn't a competitive contest. If anything, it's a highly social one. Genetic and cellular self-restraint during development and homeostasis are natural, but they aren't natural selection. Natural selection comes at an organism from the outside and delivers the bad news coldly, differentially favoring *others* with more suitable genotypes for their circumstances. Natural selection may have contributed to the evolution of the phenomena of apoptosis and repressed gene expression in this way. But today these self-restraining mechanisms are not about selection among competing cells in the body. They are not being passively screened for success nor competing to survive in a Malthusian struggle for limited resources. The apoptotic cell expresses suicidal genes and responds to other cells' inducing signals. The victim presents its own knife.

The reason the structural scaffolding produced during the development of tissues and organs is removed by apoptosis is not that the cells are too expensive to keep. Getting rid of the scaffold is how organs are sculpted. A form of selection differentiates between scaffold and structure for proliferation, but "selection" is probably a misleading word if it suggests the outer Darwinian world.

The standard definition that evolution is change in gene frequency generally does not apply within the body. Differential proliferation among cells in the embryo is not a matter of their genotypic fitness in a competitive ecological world. It is their location in the cooperative world of embryological space and time, because evolution on the developmental scale is due to change in gene use. There we can add "...or non use" because what we are depends much more on what we aren't. A cell's gene-use fitness can also change as it responds to conditions. Genetic restraint is a constructive characteristic of organized life even if, for a given gene or a given cell, it means not doing or, worse, not even being.

Evolution involves creative destruction on both the long- and short-term time scales. The long-term evolution of social behavior in organisms includes competitive selection that screens unique, random, and hence undirected mutational variation. But the short-term social behavior of cells within organisms is repeatable, patterned, and even reversible. Change in a collection of cells that we call an organism, such as a person, is *directed* through signaling by hormones or growth factors of many different kinds, which is anything but random. If it is a challenge on the evolutionary time scale to understand how random change leads to orderly adaptations through unwilling survival differences, the challenge on the developmental scale is to understand how directed change leads to orderly organs and tissues through willing, sometimes self-initiated, survival or expression differences.

Long-term evolutionary change is usually very slow and rather minor at any specific time, but genetic self-restraint and cellular self-destruction are pervasive and major all of the time. After a few generations of developmental time, the changes among cells that produce very different tissues are vastly greater than the changes in organisms after a comparable number of generations in evolutionary time. A brain is as different from its adjacent braincase, though made by the same genotype, as the difference between a baboon and a bonobo, though they're made from genotypes that have had tens of millions of years to accumulate differences. So when it comes to understanding evolution, the processes generating changes within organisms are as important and challenging to understand as those that take eons to do their work.

In reaction to the strongly individual-focused nature of sociobiology, some authors are revisiting the old disputes to argue that selection occurs on many different levels, suggesting broader conditions by which social behavior could arise.[13] Such questions will probably remain in the realm of speculation, since we can't observe what made differential survival in the past or study what didn't evolve. But we *can* study what makes differential cell or gene use in the present. The underlying mechanisms are so old and highly conserved that even in anthropology, where we can't experiment on our primate subjects or ourselves, we can use model experimental systems like the mouse to understand how we are assembled and maintained by selecting which genes shall be used and which cells shall live. A major frontier lies in indirect but evolutionarily connected research that ties comparative genome sequence and gene expression analysis together with embryological development to generate an understanding of the death wishes of life.

Clarissa is an extremely leisurely experience of a bygone era. It is frustrating, because Clarissa's dedication to self-sacrifice is so unnecessary. The morbid gesture of buying her own "house" and storing it in her bedroom showed her total commitment to a needless death for what's right, even if she was innocent of

doing what was wrong. Unlike Clarissa, the pervasive forms of self-restraint and self-destruction in cellular life are not needless if the organism is to function as it has evolved to function. But just like Clarissa, the affected cells or genes are innocent of any wrong, but are willingly repressed for the cause of what's right.

NOTES

I welcome comments on this column: kenweiss@psu.edu. I have a feedback and supplemental material page at http://www.anthro.psu.edu/weiss_lab/index.shtml. I thank Anne Buchanan, Sam Sholtis, and John Fleagle for critically reading this manuscript. This column is written with financial assistance from funds provided to Penn State Evan Pugh professors and a grant from the National Science Foundation, BCS 0725227.

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