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The Clergyman's Wife and the Parrot

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Things from the past are sometimes repeated when you least expect it.

The so-called central dogma of biology is that DNA sequence is a code that specifies amino acid sequences via a messenger RNA (mRNA) intermediate in a one-way feed-forward transfer of information. It's curious that scientists, who proclaim that everything is always open to question, would name one of our views a dogma, though it is certainly a well-established bedrock of biology that our genome hides, like the Prince of Pompadoodle, "behind a castle wall, behind a moat, behind a guard, of twenty soldiers tall," because "somewhere in the palace was a cur who'd seek his end!"[1] Chromosomes are tucked safely inside the protective barrier of the nuclear membrane, where their genes are transcribed into messenger RNA copies. Those copies leave the inner sanctum to venture into the dangerous world of the cytoplasm, where they are translated into amino acid sequences, which form proteins. The mRNA can be buffeted, degraded, and otherwise abused by cytoplasmic curs, while the princely integrity of the DNA itself is protected as the unchanged progenitor of the Dynasty.

Actually, the central dogma does not require that DNA be physically guarded in this way. Bacteria are doing just fine without a nucleus (they'll dance on all our graves, in the end). Instead, the protection is by a logical rather than physical moat: DNA is used as a stable source code to manage the changing operational material of a cell's life. This has been viewed as a universal characteristic of genomes and in that sense is a dogma, I suppose. But evolutionary theory could easily withstand the Reformation that would follow the discovery that the dogma is not just so. What is much more critical to the current theory of life is not that DNA is unchangeable, because mutations have to occur at least occasionally as the fuel of evolution, but rather that no such change is instructed by the individual's experience in a way that specifically improves its future prospects. Evolution is not teleological: It has no long-term goals. The inviolate credo is that genetic change is random with respect to any specific needs that the environment might present, and such variation is screened by the experiences of future generations to proliferate if it is helpful (natural selection) or lucky (genetic drift).

A feedback of experience that modifies the DNA sequence in a specifically adaptive way would be that ultimate evolutionary *bête-noire,* Lamarckian inheritance. Most life scientists and even social scientists, including anthropologists, explain Lamarckian inheritance with lampooned images of giraffes mightily stretching their necks to reach the high leaves in a way that changes their genes so that they produce neckier offspring. That's an inaccurate textbook caricature of poor Lamarck, as you can easily see for yourself by actually reading his 1809 book *Philosophie Zoologique,* available in English—and don't worry, you won't be heretically contaminated.[2] Though ridiculed as a mystic by many, including Darwin, who had a vested interest, Lamarck anticipated most important aspects of Darwin and Wallace's theory of evolution, only he did it 50 years earlier. (Darwin knew of the work and later suggested similar mechanisms of inheritance.)

Lamarck stressed that his views were purely materialistic, not animistic, but he did believe that what an organism does during its life is transmitted to its offspring (today we'd say "in its genes"). This quite sensible way to account for familial resemblance can be traced at least as far back as Hippocrates, 2,400 years ago. Because Lamarck's species modified their nature according to their needs, his "tree" of life (Fig. 1), perhaps the first ever drawn, did not include extinction. If he had had the advantage we have, of a better fossil record and the evidence of the dodo and passenger pigeon, he would have had to accept that some lineages simply can't stay with the program. But his idea that evolution is the result of striving to do well in one's circumstances seems obvious if you think of what we see in everyday life: We do strive to do what we can do, and we do it with future objectives in mind, including objectives for the success of our children. To modern biology, this is a genetic illusion based on what we see in our short lifetimes compared to what can happen slowly over evolutionary time. According to the central dogma our behavior, or at least that of nonhuman species, who can't set up college tuition savings accounts, is based on what we are, not on what we want to be.

Perhaps because of its intuitive appeal, and despite the central dogma, many investigators have searched for plausible Lamarckian mechanisms that would, after all, give organisms a

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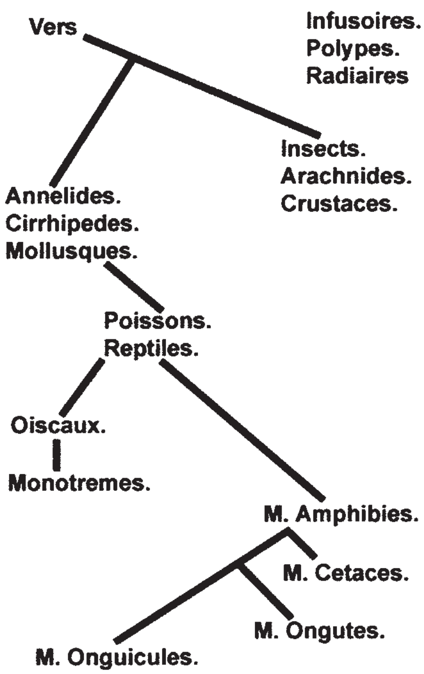

Figure 1. Lamarck's version of evolution: a "tree" with no dead branches.

marvelously quick way to adapt to changing circumstances. Some recent claims have reached at least a kind of credibility. These claims include evolvability mechanisms, by which bacteria or even complex organisms under environmental stress generate high rates of mutation in parts of their genome that code for proteins in which variation might be responsive to the stress. Immune resistance and metabolic response to nutrient stress are examples. Even if these have elements of transfer from experience (stress) to genome, the idea remains mainly Darwinian. The mutations are random relative to the specific stressor, and it's classical natural selection that favors those whose new state is able to survive.

LIFE-EXPERIENCE DOES FEED BACK ONTO GENES

At the heart of Lamarck's ideas was the inheritance of acquired characteristics. If evolvability systems are interesting and hint at, but don't achieve, real Lamarckian inheritance, in recent decades we've discovered more direct and fundamental lamarckian-like aspects of life, ones that are well known and not at all controversial. (I use lower-case "lamarckian" to depersonalize the word.)

Embryogenesis, homeostasis, and other dynamic affects on cells' environments—that is, their experience—do affect their genomes.[3–6] You are a complex organism only because your cells are differentiated; some make eyes, others make hair. That comes about through differences in the subset of its 30,000 genes that a given type of cell actually uses. During development, cells detect signals in their external environment, some of which are secreted by other cells. Cells respond to these signals by changing the genes they use, activating some and silencing others. That's how enamel and dentine layers differentiate in a tooth germ, how intestines form absorbing or secreting cells, and so on. These changes in gene expression are brought about by modification of the nuclear DNA. The changes are directed, in a meaningful sense, in function-specific rather than random ways. That's why, no matter how nasty you may be, your heart's in the right place. These changes acquired by cells' experience are inherited, too: When the cell divides, its daughter cells retain the parent cell's gene-expression pattern until circumstances cause that pattern to change.

The fact that this is how the single cell of a fertilized egg is turned into a whole organism has, in the last couple of decades, been at the center of huge advances in our understanding of the genetic basis of development and homeostasis. In fact, a greater fraction of the genome may have to do with regulating gene use than with coding for proteins.[5] This is not Lamarckian in the sense of cells "striving" to become fingers or ears, and it does not violate any evolutionary premises. Rather, it's about generations of cells within organisms, not generations of organisms. It may have transformed what we know about how genes work, but it's no threat to our overall evolutionary "paradigm." But something has recently been reported that, if true, adds a previously unknown phenomenon that somewhat reverses the genetic and evolutionary dogma.

"I DON'T KNOW WHERE YOU PICK UP SUCH EXPRESSIONS," SAID THE CLERGYMAN'S WIFE TO THE PARROT[7]

It must be tough being a clergyman. You always have to watch what you say, because weak moments from your forgotten past can come back to haunt you. The past does not present such a problem to organisms because, as per the central dogma, the flow of evolution is strictly forward in time. Or so we used to think.

The mustard-family plant *Arabidopsis thaliana* is a favorite laboratory-model species in plant biology. Like laboratory mice, *Arabidopsis* is small, cheap to maintain, and has a short generation time. Many botanists work with this species, including a group at Purdue, who made a striking finding in the course of experiments to understand the genetic basis of organ development.[8,9]

They bred plants containing a mutation that caused the parts of the flower to remain fused instead of opening normally. After a couple of generations, a percentage of these mutant plants surprisingly produced offspring that reverted to the state of their normal great-grandparents (Fig. 2). This was because the plants had precisely corrected the mutation back to the original normal DNA sequence. The striking thing is that the correction occurred in plants that no longer had a copy of the normal gene to use as a template to know how to make the correction or even what the ancestral state had been. This reversion to an ancestral DNA sequence could not be due to known error-correcting mechanisms, occurred too often to be a chance reverse mutation, involved only correction of current variation back to missing ancestral states, and occurred in other genes in these plants. Most curiously, reverse mutations also occurred in parts of the genome that don't even code for protein sequence. With typical melodrama, the news media immediately likened these new findings to the kind of "striving" for which Lamarckian inheritance is known. The plants were seeking to be like their ancestors, which, like your ancestors and mine, had obviously been at least partly suc-

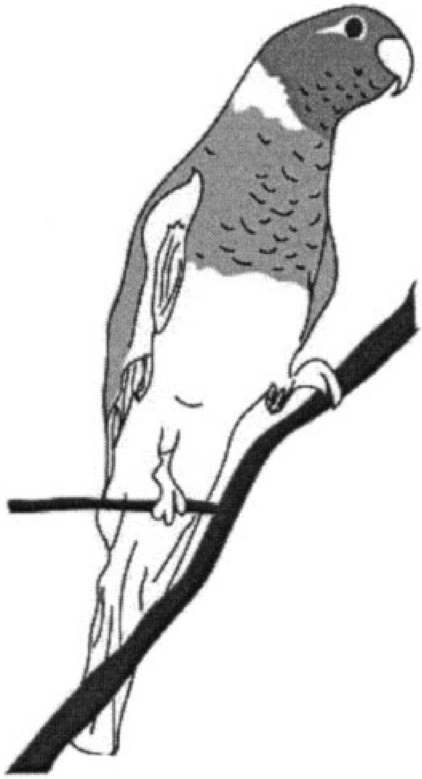

Figure 2. Teller of tales.

cessful in life. Had they not, none of us would be here to tell the tale.

What mechanism could enable this self-correction? At present we can only guess. These days many geneticists' minds are focused on gene-regulating mechanisms that are brought about by types of RNA that aren't involved in protein coding, but that have the ability to bind to DNA. One, called Xist RNA, literally coats and inactivates X-chromosomes in female mammals, leaving only one active X in any cell, to match the single X chromosome in male cells.[10] Similarly, telomeres, the ends of chromosomes that protect them from degradation, are established and maintained by RNA that binds to DNA sequences there.[11]

The Purdue investigators speculated that a previously unknown reserve pool of DNA-binding RNA can survive at least two generations without being used (that we know of), to provide a memory bank of prior DNA sequences. This is a logical extension of the fact that RNA is copied from, and hence accurately matches, a DNA template. I personally can't remember a face or name for more than a few minutes, but what we could call *anamnestic-RNA* (aRNA) might wait in the wings for a few generations and then bind to its corresponding DNA in the plant nucleus, triggering repair mechanisms to detect the DNA–aRNA mismatch (the mutation) and correct the DNA. This is speculation, but large pools of nonprotein-coding and previously unknown RNA are being discovered and seem to have important uses.[12]

This remarkable result is already receiving the scrutiny and skepticism it deserves. It goes so against current biological theory as to be widely dismissed as an awful publishing decision by Nature. It is easy to find reasons for doubt. For a pool of "aRNA" to last several plant generations, it must be replicated to avoid being diluted out of existence over many cell generations between the original mutant seed and the cell on some stem of a grandchild plant that makes the correction. How and where is this aRNA replicated? Also, the investigators found that 5%–10% of their bb plants (i.e., bad/bad genotype with no normal B), reverted to a normal trait, and of these 101 of 102 had become Bbs. But if a bb plant has a 5%–10% chance of reverting a b to a B, why didn't at least 5% of them correct both their bs to become BB? Discussion and possible alternative mechanisms, but as yet no refutation, have begun to appear (R. Pruitt, personal communication).

I'm writing in September, and by the time this is published the claim may have been refuted. But if it does prove true in *Arabidopsis,* it probably exists in other plants and, based on recent experience in genetics, we can expect some form of the phenomenon in animals, including mammals. This is because important genetic mechanisms are often deeply conserved, used and reused in different ways. Similar genetic strategies have often evolved independently in different branches of life.[6] Since self-correction appears to be a genome-wide rather than gene-specific ability in *Arabidopsis,* its impact might affect complex traits due to many genes as well as simple single-gene ones.

There's nothing new about traits skipping generations, so that a person appears to revert to the state of one of his ancestors. That's what recessive traits are, as Mendel first formally explained. In a similar way, traits due to the interaction of many genes might appear only occasionally, in unusual multigene genotypes. (People have explained Bach and Mozart and Michael Jordan in that way.) In these instances, the underlying genetic variation is always circulating in the population but is expressed only in those genotypes. That's very different from the *Arabidopsis* case, in which an ancestral DNA sequence no longer in the population is changed back to that specific former state.

Are there human traits that seem to disappear and then reappear that might be due to this kind of mechanism? If so, our usual gene-finding approaches won't identify them, because those methods assume that genetic variation is faithfully transmitted from parent to offspring. That could account for problems we have in forming genetic explanations of complex traits. Further, our speculations and reconstructions of interesting traits and their evolution are built on classical notions of inheritance and adaptation. Will we have to change these and, if so, will new understanding result? It's far too early to tell. But think what that would do to our attempts to understand the nature of primates, including ourselves. How many of our traits, inheritances, and behaviors might have gained evolutionary benefit from an ability to reconstruct states that were successful in the past?

ON REMEMBRANCE OF THINGS PAST

Marcel Proust wrote that the smell and taste of things from the past, like those of madeleines (since then known as the cliché cookie), long linger as potential triggers of streams of memory. But if the aroma of mustard might bring up memories of picnics past, mustard's memories of its own past won't bring new kinds of adaptation to its future. The core characteristic we tend to associate with evolution is future, not past, adaptation. So we might call what has been discovered reverse, or pre-verse (or perverse?) lamarckism. It is an organism

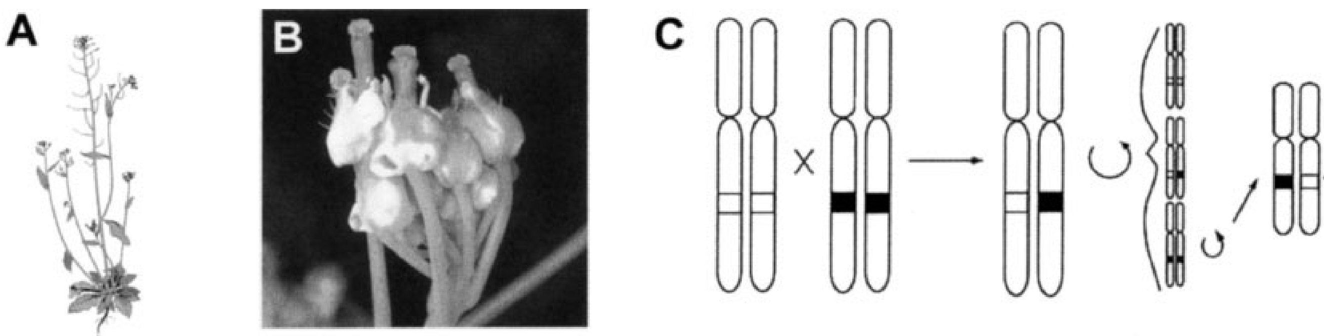

Figure 3. *Arabidopsis* self-corrects. A. The mustard-family plant (http://ukcrop.net/agr). B. Flowers in mutant plants fail to open (//news.uns.purdue.edu/UNS/html4ever/2005/050323.Pruitt.inheritance.html). C. The plant's surprising self-correction: Two copies of each chromosome are present in the cell. Left to right: Cross between normal and affected plants; open square, normal gene, black square, mutant gene; these plants are then "selfed" (circular arrow), nonsexual reproduction in which seeds have two random copies of the plant's own genes, yielding 3 offspring types; when selfed again, a fraction of the homozygous mutant offspring (lower type) restored the normal grandparental gene (asterisk). Drawing by A. Buchanan.

rummaging through its wardrobe to try on something that at least used to be fashionable.

This might help explain the kind of conservatism associated with the long periods of morphological stasis sometimes observed in the fossil record and that was controversially dubbed punctuated equilibrium.[13] This aspect of evolution is now known to have been exaggerated at best, but seemed to be inconsistent with the classical Darwinian notion (dogma?) that natural selection drives continual incremental change, ever-refining the fit of organisms to their environmental circumstances. If those circumstances didn't change, organisms would also resist change. Did cockroaches and horseshoe crabs consult their personal histories to ensure they stayed the same for so many eons?

Restoring ancestral sequence would seem to be a rather automatically adaptive and hence safe way of life. If the *Arabidopsis* story is true, and if it has anything to do with the plant's long-term history, it would be a kind of evolutionary bet-hedging. Under most circumstances, using what recently worked may not make you better, but could be a good, if conservative, strategy. One can see how classical natural selection could favor organisms that had the ability to invoke a successful past. In fact, that has happened. I alluded earlier to DNA repair mechanisms, of which many are well known. Such mechanisms presumably evolved because mutation is usually a threat to the existing order. But this kind of DNA repair happens basically at the time of the mutation, not generations later, which is what is remarkable about the *Arabidopsis* findings.

Such abilities may have evolved during stable environmental times in which the past really was prologue. But like armies that prepare to fight their previous war, it would be a terrible strategy, an evolutionary Maginot Line, when environments change. And whatever this active DNA reversion turns out to be, we know that even roaches and crabs continued to accumulate divergence at the DNA sequence level, no matter how static their appearance. Indeed, evolving not to evolve would stop evolution in its tracks if it worked perfectly. That would be a lethal situation, since environments are often, if not always, changing. In reverse lamarckism, all lineages, looking backward instead of forward, would go extinct.

It will be important to learn just how memory-based genetic correction takes place and how widespread it is in nature. But it's no threat to our basic notions of adaptive evolution. A parrot may affect a clergyman's present success by reviving his past failures. But that's the opposite of a mustard plant, which echoes its successful past to correct its present failures. A main lesson of evolution is that in the long run there can only be echo of success. Failures are the mutes of history.

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.html. I thank Anne Buchanan and John Fleagle for critically reading this manuscript.

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