

Week 4: Evolution: Genetics, Epigenetics and the Environment

May 8, 2018

“Imagine landing a time machine 3 billion years ago in shallow coastal waters. The first thing you notice is that the sky is not blue, but a dull hazy red, a touch reminiscent of Mars. The quiet seas reflect in shades of red. It’s pleasantly warm in this haze, if too misty to see the sun clearly. On land not much catches the eye. The rocks are bare, with damp patches of discoloration here and there, bacteria clinging precariously to their extreme terrestrial outpost. There’s no grass or vegetation of any sort. But marching through the shallow waters are scores of strange domes of greenish rock. Apparently the work of life, the tallest are a metre or so high. A few familiar rare structures are still found in the most remote and inaccessible bays on earth today: stromatolites. Nothing else stirs the waters. There’s no fish here, no seaweed, no scuttling crabs, no waving anemones. Take off your oxygen mask, and you’ll soon understand why: you’ll suffocate in minutes. There’s barely any oxygen, even close to the stromatolites. Yet their blue-green bacteria, cyanobacteria, are already beginning to lace the air with traces of that hazardous gas. In a billion years, their emissions will finally turn our planet vivid green and blue. And only then will we recognize this bare place as home.”

From Lane N. (2009) *Life Ascending: The Ten Great Inventions of Evolution*, W.W. Norton & Company, New York London, Page 263***

Introduction

One of my favorite BBC programs is based on the veterinarian *James Herriot's* book series, '*All Creatures Great & Small.*' The story chronicles the adventures of Herriot and his colleagues in a rural, mostly large animal veterinarian practice in York in the 1930's through to the 1950's. There were many examples of those vets being called out to deliver sheep, calves and fowls, whose births were held up for one reason or another and needed the help of a vet help to deliver them. But for a city person like me, one of the most striking observations was that the newborns, within minutes of birth struggled to their feet and made their way, if a little awkwardly at first, toward their mother's breast and the first meal. Within hours they were soon able to get about like old hands. Standing and walking was clearly innate from the get-go and genetically dictated with no need for instruction. Clearly the underlying neural networks for standing and walking were already in place.

Contrast that to humans. Human babies are developmentally premature relative to the babies of other primates at birth. The problem is that in order to get their rapidly growing brains through the birth canal, human babies must be born, developmentally speaking, much earlier, than is the case for our living primate relatives and was the case for our pre-Homo ancestors. The result is that the period of dependency on parents and others in the community lasts much longer for modern humans. That developmental immaturity of the human brain at birth goes a long way to explaining why human babies are so helpless compared to other mammalian species at birth, and why it takes so long, compared to other mammals, for human infants to initially lift their head, then over a period of several months progress through rolling over, to pulling themselves up, eventually stand without support and later walk, and even the last is wobbly for a few months.

No one teaches babies how to roll over, crawl, stand or walk – its all innate and genetically determined, although quickly improved on through endless repetition and fine-tuning the underlying neural networks. Practice, practice, practice underpins learning any highly coordinated motor activity as anyone who has watched babies progress from near helplessness, to

walking and eventually running, can attest. And I might add, the same probably holds true for most learned skills.

Shortly after birth, infants begin to turn toward and fix their eyes on their mother's eyes and to a lesser extent their mouths. That this behavior is strongly dictated by genetic influences was shown recently by studies of twins, in whom the frequency and duration with which babies fixed their eyes on their mothers eyes was compared in identical twins in which the frequency and duration of visual fixation on mother's eyes was nearly identical for twins, somewhat similar for non-identical twins, but there was no correlation between unrelated babies of the same age. It seems then that early on, genes trump other influences in infants. However it isn't long before strong emotional bonds (or lack of) between mother and child and soon cultural behaviors, begin to heavily influence the further development of infants and children.

Richard Tremblay from the *University of Montreal* showed that children emotionally deprived in infancy and early childhood may develop antisocial behaviors, which last a lifetime. Later genetic studies of the same children showed that many of the children revealed epigenetic changes, expressed as methylation of bases in their genomes, not seen in healthy children. And even more worrisome was the observation that such epigenetic changes may be passed on to future generations. That's an ominous observation, but illustrates that the emotional scars of one generation may be passed on to generations to follow. And that's in addition to whatever continued regressive cultural influences might continue. These observations raise important questions about the effects economic and cultural ghettos of the kind often seen in large cities might have on future generations. It's certainly a social, political and moral question worth exploring.

One of the best studies of the effects of training and epigenetics on behavior is that of *Dimitri Belyaev's* study of breeding wild foxes for docility. See the essay, '*Domestication: Dogs, Foxes and Humans*' below.

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Domestication: Dogs, Foxes and Humans

The Russian, *Dimitri Belyaev's* background in breeding foxes for their fur was common enough in Stalin's Russia and elsewhere in the world where furs were prized as much or more for their beauty as warmth. *Belyaev*, however had other ambitions. He wanted to find out whether the naturally aggressive and wary behavior of wild foxes could be changed into something akin to household dogs - the long domesticated descendants of wild wolves. He was a trained geneticist; a political and scientific challenge in Stalinist Russia where the view that culture – not genetics – dictated behavior held sway and scientists with contrary views were subject to losing their job or much worse.

Belyaev's interest in the subject was rooted in the observation that some animals were readily domesticated by contact with humans, beginning with wolves and much later others including sheep, goats and cattle. However not all animals can be domesticated. Zebras for example- have so far resisted all efforts to domesticate them. Domestication of wolves began approximately thirty thousand years ago and was a two-way affair that benefited both. The relationship probably began with wolves hanging around human campsites, scouring for food. But whatever the prompt, it probably wasn't long before the two forged close bonds with one another. Wolves, and what would become the earliest domesticated dogs, probably offered warning of approaching predators and strangers, partners in hunting and may have offered a measure of protection, while humans offered a reliable source of food from the hunt, and each offered the other companionship. The two species coevolved over thousands of years – both acquiring along the way the genetic where-with-all for digesting grains. So valuable was this relationship that there is evidence that dogs and humans were buried together in a fashion strongly suggestive that a deep personal relationship had developed between the dog and human many thousands of years ago.

Modern day wolves remain wary of humans and even if raised and fed as pups day and night for weeks by the same person, usually retain their predatory instincts and may turn on those who raised them given the right cues such as running after or chasing them (Gorman, 2017). So turning

wolves into dogs just isn't in the cards. Some scientists have speculated about whether deletion (or epigenetic inactivation) of certain genes, related to some of the 26 or so genes lost in Williams's syndrome in humans: a disorder associated with hyper-social behavior (together with other features such as distinctive facial features and mild mental retardation). Maybe so, but there's no genetic evidence as yet to support such a far-fetched hypothesis.

Cats were more recent domesticates, beginning about 9500 years ago or about the same time humans took up farming in the Middle East. In their case, tameness and a willingness to hang out with humans, whether for food or company, was associated with changes in some of the 281 genes recently found to differ between Near Eastern and European wildcats and domestic cats.

Red foxes in urban areas are solitary animals that prefer to keep to themselves except for mating and caring for their young. That was certainly my observation in Niagara-on-the-Lake, Ontario where for several years red foxes raised their frisky cubs in a culvert beneath our driveway. Once I managed, to hand-feed one of the adults. Like the wolf in the movie 'Dances With Wolves', the adult fox approached the wiener dangling from my outstretched hand, cautiously and hesitantly, before finally grabbing the wiener - not my fingers or hand - and running off. That was as far as I got. There was no overt aggressiveness but both adults kept their wary heads and eyes on my wife and me when we were in the garden. Then one day they promptly pulled up stakes with their cubs when a strawberry festival was held half a block away and heavy car and people traffic clogged our street. That was the last we saw of them that year or any other matting foxes in the years to come. In captivity foxes are famously very aggressive and snarl and sometimes try to bite the heavily gloved hands of any caretakers who get too close. Glad I didn't know that when I offered the wiener.

It was the wariness, and aggressiveness that *Belyaev* hoped to breed out of the foxes by choosing the least aggressive females and males in successive generations for mating. He and his key associate *Lyudmila Trut* succeeded well beyond their hopes. For within a few generations the cubs and later

adults became increasingly calm and comfortable with their caretakers to the point where some could be picked up and seemed to look forward to human company. Soon some began to wag their tails in response to their caretakers. And it wasn't long before selected foxes could be taken for walks, on leashes initially, and later free to roam, would come when called. Eventually the adults took on a different appearance; snouts became shorter and rounder, legs shorter and stouter, the ears, floppier and the pattern and color of the fur changed. In short they began to behave and look like domestic dogs – all at a pace impossible to reconcile with the usual slow accumulation of random mutations so characteristic of natural selection. It was a case of evolution on the fast track.

Behavioral and anatomic changes such as these are complex and probably involve many genes. In the natural state fox pups are playful, if frisky with one another, but as they mature and grow into adulthood those genes favoring wariness and aggressive behavior and the anatomical features of wild foxes become activated. In the case of foxes bred for dog-like friendly behaviors, the genes underlying those behaviors and their associated dog-like anatomic features persist into adulthood while those, which in the wild would have favored 'wild' behaviors and anatomic features, remain silenced. Thus the underlying changes in the fox genome involved not the acquisition of new genes but 'switching genes' – genes tasked with activating or silencing other genes – which in the case of the silver foxes affected not only their behavior - but also their appearance. The changes observed in response to intentional selection for docility resulted from spreading existing alleles, which favored docility and their associated physical changes more widely throughout successive generations and silencing other genes favoring aggressive behavior. This hypothesis was supported by whole genomic studies in the prefrontal cortex of tame foxes which revealed two hundred and eighty 'active' genes, which were present but silent in aggressive foxes. On the other hand, fifty-five other genes, which were silent in tame foxes, were found to be active in aggressive foxes.

There's more to the story. It turns out that docile generations of foxes had lower levels of 'stress' hormones such as cortisol and more of the feel good 'calming' hormones such as oxytocin and melatonin and the

neurotransmitters, serotonin and dopamine. All this fits with a brain including a hypothalamus and forebrain geared by intentional selection toward docile behavior.

Self-domestication is not confined to cats and wolves. Recent evidence suggests that it may have played an important role in human evolution by encouraging a willingness to cooperate with others and wider social networks, to better survive in harsh environments where social cohesion was critical to survival. These behavioral changes were associated with anatomical alterations such as flatter faces, smaller jaws, and less prominent brow ridges. The latter changes began to appear in the last 80,000 years according to studies that compared the skulls of 13 early Homo sapiens living before 80,000 years ago, with 41 modern humans living between 36,000 to 10,000 years ago, and recent human skulls.

Dmitri Belyaev's and *Lyndmila Trut's* studies are the key to understanding how intentional selection (and self domestication) - unlike natural selection - can dramatically change behavioral and physical traits within a few generations by selecting from among the pool of genes already present in the genome, as was found to be the case of the silver fox studies. The fox studies hint at how cultural and environmental influences acting over several generations, might in humans, alter the 'active' status of whole suites of closely related genes, and how the changing status – active or silent and the timing of that status - might be passed down through successive generations in response to selective environmental, and cultural pressures.

Humans may have domesticated themselves when they switched from the relatively small groups characteristic of hunter-gatherers, to more settled existences and adjusted to the added pressures of living among larger groups including more casual acquaintances and strangers. All of which probably put a selective premium on those skills needed to navigate the much more complex social landscape of urban life compared to the simpler much more familiar day-to-day social landscape of hunter-gatherers. Along the way those changing social and environmental pressures, acting over many generations, probably shaped who we became and are today.

But as for the future, who knows what's in store? It depends!

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Evolution on the Fast Track – Foxes and Cancer

Evolution is often portrayed as a slow affair – the result of a series of spontaneous mutations, most of which are neutral, some bad and some offering some advantage such as the capacity to process lactose or tweaking some other favorable physiological or anatomical trait. Mutations, although chance events, tend to occur at a more or less steady rate over thousands of years. These rates are steady enough to calibrate for time and estimate our genetic distance from our last common ancestor. In the case of counting mutational differences between mitochondrial DNA samples taken from modern day humans living around the world, this meant that ‘mitochondrial Eve’ as she became famously known - along with other females of her time - were estimated to have lived somewhere in Africa roughly one-hundred and fifty thousand years ago. Other estimates using ‘Y’ chromosomal DNA and nuclear DNA came up with similar estimates to when our species emerged in Africa so long ago and are in good accord with evidence from the fossil record pointing to when anatomically modern humans emerged in Africa. The same technique can be used to estimate the genetic distance between any two species – studies which conclusively show that all species are related to one another – its simply a matter of how far back we need to go to find that common ancestor.

But evolution can occur much faster – in a matter of thirty to fifty generations in the case of foxes intentionally bred for docile behavior. Within as few as six to ten generations, wild foxes, which are normally wary and very aggressive toward humans could be handled without fear of biting, and within a few more generations, became pets and very much like domestic dogs in their behavior. These behavioral changes were accompanied by changes in their ears – they became floppy – and the color and texture of the fur changed too. The changes were much too fast to be explained by selection acting on chance mutations. There had to be another explanation and there was. What happened was that selection for certain traits – in this case docile behavior - activated preexisting gene variants favoring docility while at the same time, other genetic variants favoring aggressive behavior, were silenced by so-called ‘switching’ genes. So major behavioral and anatomical changes can occur without mutations.

Rapid adaptive changes occur in other species including some fish in Lake Victoria in Africa but that's another story for another column.

There are plenty of examples of evolution on the fast track but none more impressive than cancer cells. There is strong evidence that cancer is caused by runaway cumulative mutations in cells in response to natural aging, radiation – think the sun here and some forms of skin cancer – and exposure to any number of carcinogens in the environment. Some genetic variants of the BRACH1 gene may be passed on from generation to generation, and greatly increase the risk of breast and ovarian cancer.

Normally cells live in communities or in the case of the bone marrow and lymph nodes begin in communities, and within those communities cells communicate with one another using molecular signals and receptors to control their numbers and behavior. However some harmful mutations may develop which effectively mask budding cancer cells from these constraints. The result is that some cells escape those natural limits on their multiplication. Whether they succeed or not depends on whether the body's immune system recognizes them as 'foreign' and if so, destroys them. However, even here, further mutations may effectively mask the cancer cells from the immune system. These and other mutations eventually create runaway groups of renegade cells, capable of seeding themselves throughout the body and impervious to all the body's natural defenses. And if that were not enough, the same adaptive resiliency of the cancer cell to the body's defenses often proves remarkably nimble at finding solutions to get around various chemotherapy drugs. So a favorable response to a new or novel drug, including one of the very expensive immunotherapeutic drugs designed to attack specific molecular markers on cancer cells, may work marvelously - only for surviving cancer cells, perhaps better adapted to resist the drug, to expand into the vacuum and the cancer returns with a vengeance. The situation is akin to what happened after the great extinctions in Earth's past when anywhere from seventy to ninety-five percent of species were killed off and surviving species quickly moved into the niches left behind. That's what happens in cancer, surviving cells – even a few of them – escape the chemotherapeutic extinction – and go on to prosper. Its Darwin on the fast track – here natural selection acting quickly to choose those species of cancer cells, which survived successive

onslaughts of chemotherapy, radiation and whatever else we throw at them.

Now that whole genomic sequencing has become much cheaper and more widely available it's obvious that the genomic roadmap of most cancers rapidly changes. The latter can occur so quickly with some cancers that it's really difficult for oncologists to keep up. Sometimes simultaneously attacking several vulnerabilities of the cancer works – but not always and not nearly enough for many patients. One lesson to be learned is that catching cancer early before most of those nasty mutations have taken place is the key to success. And here there is hope; because it turns out that the genomic fingerprint of many cancers can now be detected by blood samples, years before the cancer makes itself known by an obvious mass or with the usual tests. There's a recurring theme here isn't there – for most diseases, its better to get to them as early as possible and that applies to Alzheimer's disease and cancer.

W.F. Brown

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Poverty, Starvation, Emotional Deprivation and the Brain

These days poverty and starvation are common in conflict zones in Nigeria, Sudan, Ethiopia, Syria, Yemen, Bangladesh and other parts of Southeast Asia to name a few. Scenes of skeletonized infants and young children near death from starvation and disease are horrific and the consequences extend well beyond the present for those children, who by luck or intervention, somehow manage to survive.

For it is in utero and early childhood that the brain's platform and evolving networks of nerve cells is laid down. Evidence suggests that the brain begins to learn in utero. Shortly after birth babies begin to track their mothers eyes and to a lesser extent their mouths. Recent twin studies in which the eye movements of young babies were tracked suggest that genetics dominate this early phase. However it isn't long before the social environment, language and culture in which the child is immersed begin to shape the development of the brain and infants begin emulate behaviors such as persistence from their mothers. The natural genetically choreographed development of the brain depends on lots of healthy natural stimulation and adequate nutrition. But absent the latter critical influences, and adequate nutritional support for the brain's development, the brain sometimes fails to develop properly and the consequences may be both devastating and permanent.

Evidence for the last assertion is the fact that affected children may be cognitively impaired permanently; a view supported by MRI imaging studies, which show that critical regions of the brain related to cognitive and language functions may fail to develop properly. This should come as no surprise. In adults the brain weighs less than five percent of the total body-weight yet consumes roughly twenty-percent of the body's energy. In short, even in adulthood, the brain is an energy hog and much more so in the period of intense brain development, which begins in utero and extends through childhood. Persistent malnutrition, through poor diet or repeated diarrhea or both, may put the brakes on the brain's development leaving affected children cognitively and emotionally disabled for the rest of their lives.

Emotional deprivation during early development is equally costly and associated with a similar failure of certain regions of the brain to develop normally. That's what makes poverty, malnutrition and emotional deprivation so costly – the damage to the brain, tragically lasts a lifetime. Its a powerful reason for private agencies and governments to intervene early when poverty, malnutrition and emotional deprivation most threaten the future of countries and cultures by threatening not only the survival of the most vulnerable – the unborn and very young - but the health of their brains on which the future prosperity of whole communities hangs in the balance. The Gates foundation recognizes this problem and invests in trying to stop the consequences of long term brain damage by intervening as early as possible in areas of conflict throughout the world. Unfortunately there are limits to what can be done when lawless warring parties threaten and otherwise block the best efforts of aid agencies as we've witnessed in Syria and the Sudan.

There's a Canadian side to this story. For several decades Richard Tremblay at Montreal University studied the roots of violence in the Montreal region. His studies strongly suggested that young children deprived of nurturing maternal care, were more likely to exhibit antisocial behavior and aggressiveness later in life. Follow up studies suggested that such behavior might have genetic underpinnings - not through changes in the genome, - but changes in the expression of genes mediated through methylation of bases and other 'epigenetic' influences. Whether the epigenetic changes found in the genes of Tremblay's children later in their lives played a key role in their antisocial and sometimes violence behavior later in life hasn't been resolved. However similar epigenetic mechanisms altering gene expression apparently played a key role in turning naturally wary and aggressive wild foxes into domesticated pets, when the foxes were bred for docility.

Poverty, emotional deprivation and starvation, singly and together can have devastating events on the developing brain of young children and long-term, may impede the future development and prosperity of affected individuals and whole communities, societies and nations. That's one of the reasons why on going conflicts such as those waged in Syria or Venezuela can have tragic consequences for current and future generations and are

reasons enough to double our efforts to do anything we can as a country to support international peace efforts in such regions. The cost to future generations as well as the present is too high to do less.

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Genes, Epigenetics and the Environment

Charles Darwin was the father of '*natural selection*' and less well known, '*sexual selection*' as the primary instruments, which together shaped the evolution of species including humans. At the time he was unaware of the work of the monk, *Gregor Mendel*, whose experiments, revealed the basic rules underlying the hereditary determinants of physical traits such as the color and height in plants. However it took several more decades before chromosomes, and specifically the nucleic acids, were revealed as the all-important molecular which underpinned variation within species.

It wasn't until 1952, that *James Watson* and *Francis Crick* revealed, in what most may have been one of the shortest, most revolutionary papers, in all of biology and perhaps even science. *Watson and Crick* showed the molecular template for life was a beautiful helix formed by two thin strands of nucleotides bound together in a winding staircase of complementary base-pairs, like rungs in a ladder. It turned out that the code for life was written in the order of the bases, each successive triplet coding for a specific amino acid, and strings of amino acids to form proteins. In this and other ways, DNA and RNA dictate all of the molecular machinery of living cells.

Albert Einstein, most famously, but other scientists as well have often commented on the staggering beauty of nature, whether revealed in the mathematical equations which describe the relative motions of bodies by *Isaac Newton*, the relationship between space, time and gravity or in this case of all of biology, the fundamental simplicity of the molecular underpinnings of life.

What followed in the wake of Watson and Crick's landmark study was a avalanche of information over the next seven to eight decades about how genes, acting singly and in related families, provided the underlying code for making proteins and all other structures in the cell, orchestrating the orderly differentiation of fertilized egg, into hundreds and in some cases, thousands of cells, each fitted out for specific tasks which working together form the highly complex network of relationships between cells in for

example, multicellular organisms, and finally transmitting to the next generation, faithful copies of the parent organism.

Those studies also revealed, that at the most fundamental level, that all life forms, however diverse, are related and share with one another, to a surprising degree similar genes, proteins and other molecules and systems for generating energy, waste disposal and communication with other cells. That too is beautiful.

Table 1

Percent of genes in common between humans and various species

Baker's yeast	18%
Wine grape and rice	24%
Round worm	38%
Honey bee	44%
Fruit fly	47%
Starlet sea anemone	54%
Chicken	65%
Platypus	69%
Zebrafish	73%
Dog/Horse	84%
Cow	85%
Mouse	88%
Chimpanzee	>98%

From Carl Zimmer in the National Geographic, July 2013, page 102

When *Charles Darwin* wrote, '*On the Origin of Species*' in 1859, evolution was thought to be a relatively slow affair, characterized by the very gradual transformation of species. He was aware of the role extinctions might play in evolution, and speculated in his book, whether the explosion of animal life during the Cambrian explosion of life roughly half a billion years ago might be an plausible argument against natural selection as the engine of evolution. However Darwin was unaware that the Cambrian explosion went on for twenty five million years, more than enough time for many new species including many animals, to appear. Major extinctions, for example,

might wipe out anywhere from seventy to ninety percent of species in the seas and land, opening up vast environmental niches into which surviving species can rapidly expand and diversify. So evolution can be quick – but how quick, and what are the underlying mechanisms?

E. Coli and Rapid Evolution

**Luke McNally and Sam P. Brown (2016) *Visualizing evolution as it happens: A meter-scale growth plate allows the evolution of antibiotic resistance to be tracked*, Science, 353, 9 September, Pages 1096-1097

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E. Coli, like most bacteria around today, have roughly ten times the number of nucleotide pairs in its genome and ten times the number of genes as their simpler relatives, Archaea possess. Still, compared to humans, E. Coli seems to have more than their share of genes - 4,100 compared to the 20,000 or so protein encoding genes in humans (Zimmer, 2013). Why so? Of course E. Coli, even if a gut dwelling bacteria, still has to make its own proteins, copies of its DNA and generally look after its energy and disposal needs. Even so ~4000 genes seems a bit rich. It turns out that E. Coli can indeed make do with much less: 302 genes to be exact as essential to its existence, once other, apparently non-essential genes have been “systematically shut down” (Zimmer, 2013). This finding of course raises the question about what the minimum might be for humans as well as other species. But even if relatively simple compared to multicellular organisms, E. Coli is still an extraordinarily useful organism to study because environmental challenges can be studied over thousands of generations in the laboratory economically.

The fact that the bacteria are so cheap to maintain, multiple several times a day and their genomes can be sequenced relatively cheaply, makes them prime targets for studying evolution or perhaps better for some, ‘adaptation’. For example E. Coli and other bacteria are often used to study resistance to antibiotics, a trait they readily acquire sometimes within a few generations.

One way to study the latter is to inoculate the bacteria into one end (call it the starting line) of a large nutrient-rich agar platter, into which differing concentrations of antibiotics have been injected in different locations on the platter. Using *E. Coli* genetically engineered to fluoresce; it's possible to follow the bacteria as they migrate out into the plate seeking new stores of food and in the process run into differing concentrations of antibiotic. Some migrants are stymied in their migration to seek fresh supplies of food by the antibiotic, especially at higher concentrations, while other groups of bacteria seeking food, slow down when they hit middling or even high concentrations of the antibiotic, before exploding in numbers. Sequencing the genomes of the latter successful groups reveals that most of the successful migrants had developed resistance to the antibiotic on the fly, related to the acquisition or expression of genes capable of overcoming metabolic blocks created by the antibiotic; A perfect example of evolution (or adaptation) on the fly.

E. Coli and the 12 Tribes

One of the most extraordinary studies of 'evolution at work' is the work of *Richard Lenski* and colleagues at Michigan State University highlighted by two books, "*The Greatest Show on Earth*" by *Richard Dawkins* in 2009, and "*Relentless Evolution*" by John Thompson in 2013 and a recent review in *Science*, by Elizabeth Pennisi (2013). Since those early days, Lenski and co-investigators have now rigorously tracked the evolution of *E. coli* for over fifty-eight thousand generations – more than enough time for evolution and natural selection to make themselves felt. For this task *E. coli* are ideal. They divide 6.6 times a day and they're relatively cheap to look after. But what did *Lenski* do that was so special and unique with these bacteria?

Beginning in 1988 *Lenski* and his co-investigators at Michigan State University split an ancestral population of *E. coli* among 12 flasks, each containing the same nutrient and roughly the same number of bacteria. Every day thereafter for over 25 years, one percent of the culture in each family's flask was inoculated into a fresh flask containing fresh nutrient comprised of glucose as the chief source of energy and, citrate which none were able use as an source of energy. Given that at the end of the day, each

flask contains roughly 500 million bacteria of which only a few million are transferred to the new flask, (*Thompson, 2013 Page 267*) the effect is to create genetic bottlenecks every day by winnowing out more than ninety-five percent of the bacterial population every day.

Throughout those many years and daily flask changes to follow, the investigators took scrupulous care to avoid any cross contamination between the original 12 families of bacteria separated from one another through the many thousands of successive generations to come. The 12 families were then, in every sense, geographically separate from one another; free to mutate and adapt to conditions, independently of whatever their relatives were doing in parallel family lines borne of the same ancestral group.

Each day, as might be expected, their numbers initially exploded when they were inoculated into abundant fresh nutrient, only to plateau as the food supply ran out. This feast and famine cycle repeated itself every day for thousands of generations. The ensuing more than 24 years was the equivalent of many thousands of bacterial generations (several each day) and the rough equivalent, stated in human generations, of tracing our ancestry back to the emergence of *Homo erectus* over a million years ago, well before our own emergence 100,000 to 200,000 years ago as a species. Over this more than one million-year equivalent to our own ancestry, *Richard Lenski* observed striking changes (*Dawkins, 2009 pages 116-133, Thompson, 2013 pages 263-268*). Every 75 days a sample from each bacterial line was frozen. And should something unusual develop in one of the lines, those frozen samples made it possible to work backwards to trace the emergence of the change at the genetic level and even repeat the process.

First the size of the bacteria increased steeply over the first several thousand generations following which body-size tapered off. Second the latter pattern though differing significantly between families remained true to form for each family for the next several thousand generations. This suggested that while increased bacterial size, of itself was an adaptation shared by all families, genetic solutions differed not so much in kind – although that was a possibility – as by the extent to which similar solutions

or sequences of solutions had evolved in each family. Adding strength to the latter view is the fact that when he compared two families with nearly identical changes in body size, the same genes – all 59 of them - changed in the same manner suggesting, that the same solutions to body size had somehow been reached by two families of *E. coli* isolated from one another for thousands of generations. The experiments as of 2013 had progressed well beyond 58,000 generation mark, long enough for mutations, at one time or another and perhaps many times, to involve all points in *E. Coli*'s genome through point mutations, deletions, insertions and inversions (*Thompson, 2013 Page 266*).

Most impressive was the finding that one of the families clearly and unambiguously distinguished itself at about the 30,000th generation mark by exhibiting a truly remarkable increase in body size, which once attained remained the norm thereafter. What happened? What happened is that these bacteria had found a way to use citrate as a source of energy – a source present in the medium of all the families from the outset of the study - but a source of energy none of the families were equipped to use at least up to then. This talent for using citrate corresponded to mutations in the bacteria, which required not one mutation but two – working together to produce the effect!

Richard Lenski's studies illuminate how a simple organism such as *E. coli* can be used to gain a glimpse into how evolution might work at the molecular level over many thousands of generations – something next to impossible to study over the equivalent number of generations in much longer living animals such as us.

Christoph Adami and *Charles Ofria* developed software driven simulations for evolution using digital surrogate organisms. The computer models made it possible to greatly speed up the pace of evolution by thousands times compared to *E. Coli* (*Adami, 1998*). They showed that complex traits such as the evolution of the vertebrate eye probably depend on an accumulation of multiple mutations. Since then *Lenski* and *Adami* have collaborated on studies of evolution, both digital and biological.

The *Pseudomonas aeruginosa* story

Evolution can move quickly and there's no better example than *Pseudomonas aeruginosa*. This story was recounted recently by Carl Zimmer in the New York Times recently (2013) about work carried out by [Dr. Xavier](#) and reported in Cell Reports (2013). This bacterium gets around by laying down its own gooey carpet and propelling itself about by a single tail (flagellum). In a study reminiscent of [Lenski's](#) E. Coli studies, the *Pseudomonas* bacteria, when encouraged to forage for food, developed multiple tails within a few days, the better to propel them about and thus cover more territory, find food and most importantly out reproduce their single tailed relatives. Given that these bacteria can reproduce up to ten times a day and that the evolution of multiple tails took only a few days, here was a clear example of evolution on the fast track. However just as easily, evolution may make abrupt about-turns from favoring lots of tails to reverting to one tail again when the environment favored rest rather than foraging. And all of this action could be observed through the microscope.

A similar but much more ominous example of evolution on the fast track is the case of cancer cells, which not only evolve to defeat the body's natural defenses but far too quickly, overwhelm even some of the newest most powerful genetically engineered strategies for defeating cancer (see attached essay).

Killifish

There are plenty of other examples of rapid evolution; many involve species such as the Atlantic killifish, which evolved solutions to pollution, enabling the species to survive in heavily polluted waters ([Michael Tobler and Zachary Culumber \(2016\) Swimming in polluted waters: Genomic data provide insights into the molecular basis for pollution tolerance of Atlantic killifish, Science, 354, Pages 1232-1233](#)). The solutions at the genomic level were remarkably similar in different species of killifish and suggested that species with a high genetic diversity such as the killifish are best suited to adapt rapidly because they have a larger repertoire of genetic solutions on board for solving the problems posed by the pollutants. The elected choice then rapidly spread through the population.

Poeciliid Fishes

Another remarkable example is that of the poeciliid fishes (*Rudiger Riesch and Martin Plath (2017) Evolution at the limits: Studies of fishes that inhabit toxic sulfide springs reveal mechanisms of natural selection, Scientific American, April, Pages 55-59*). These fish are remarkably capable of adapting successfully to waters highly polluted with hydrogen sulfide, a highly toxic compound which binds with oxygen in the environment, blocks the ability of hemoglobin to bind oxygen and freely penetrates the gills of fish. These fish adapted by developing larger mouths, including the lower lip and, increasing the size of their gills, all to increase the amount of oxygen they can extract close to the surface of the water. They also developed enhanced metabolic systems for detoxifying hydrogen sulfide. Similar adaptations were developed by different species of the poeciliid family of fishes in different environments. Taken together with the killifish experience, the two studies suggest that at least some short-lived fish are capable over a few generations of adapting to some pollutants in the environment.

Cichlid Fish in Lake Victoria in Africa

Then there's the remarkable story of the Cichlid fish which though found worldwide, in Lake Victoria in Africa illustrate a startling phenomenon. Over the last 500 years a single species morphed into more than 500 species, each with their own niche and traits. Some are tailored to scrapping algae off rocks, others to catching insects while yet others have huge extensible jaws, the better to suck in their prey. Some aren't much longer than an inch and others range up to 3 feet in length and their colors seem to vary all over the map. And perhaps strangest of all, some of these species seem to be able to revert to previous traits when it's to their advantage to do so. What accounts for such an explosion of diversity in such a short period of time?

Axel Meyer writing in Scientific American recently (April 2015, pages 70-79) provides some of the answers. It turns out that mutations and gene duplications are more common in Cichlids than most species. The latter allows one copy of a gene to carry on with its usual task, while freeing any

duplicates to change function and possibly even confer some advantage to the fish for exploiting some niche in their environment. Cichlids also exhibit '*jumping genes*' or gene copies which 'jump' to new locations on the gene strand; possibly to sites where they can alter the functions of their new neighboring genes. If these genetic surprises were not enough, these fish have other tricks up their genomic sleeve. For example portions of DNA, which are usually very stable and resistant to change in most species, undergo more mutations in cichlids. And going further, they have more microRNAs – bits of genetic material that can change the function of DNA - than other fishes. It all makes for a highly nimble and adaptable DNA, which by holding on to previous versions of DNA is capable of reverting to previous traits, should the environment dictate. And perhaps strangest of all, they have two sets of jaws, one in the obvious position and the other hidden deeper in the throat.

Bird Beaks

Many species are capable of rapidly changing the size and shape of their beaks – sometimes within a generation or two, in response to rapid environmental changes and the need for different beaks solve challenges in finding and accessing food (*Steph Yin (2017) Finding the Speed of Evolution in a Study of Bird Beaks, The New York Times, February 1*).

What about lizards?

Richard Dawkins (2009) draws attention to the evolution of Lizards of Pod Mrcaru. His account is worth repeating because of the rapidity and obvious magnitude of the changes. Just off the Croatian coast lie two small islets, one Pod Kopiste was populated with common Mediterranean lizards, (*Podarcis sicula*) which ate mainly insects. The other islet, Pod Mrcaru was free of them. In 1971, five pairs of these lizards were transferred to Pod Mrcaru. Thirty-seven years later Pod Mrcaru was revisited only to find that in that very short interval the descendants of the original immigrant lizards were much different. Not only were their head sizes more massive and associated with more massive jaw muscles but they now subsisted mostly on a vegetarian rather than the insect diet of their ancestors on Pod Kopiste. The shift to the more vegetarian diet was associated with the

evolution of a valve in their caecum allowing them to more effectively digest the vegetarian diet by providing what Dawkins likens to a fermentation vat to aid their digestion of the greatly increased cellulose load of their now largely vegetarian diet. It really is quite a remarkable story of major changes in appearance and function of the head and gastrointestinal system over the relatively few years since leaving their ancestral island.

Recent Evolution in Humans – Some examples

Resistance to malaria

Lactose tolerance

Skin pigmentation

Epicanthic folds

Hemoglobin in Himalayas

Distinctive regional skeletal adaptations

Shape of the nose and mouth

Controversial cognitive changes, Ashkenazi Jews, Mandarin class in China

Smaller brain in the last 10,000 years

Lighter skeletons in the last several thousand years

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Genetics Beyond Base Sequences: Epigenetics

In recent years it has become apparent that there's a great deal more to genetics than simply the information written in the sequence of bases of our DNA. Much of DNA in the genome is made up of genes whose job has much more to do with turning on or off genes or whole suites of genes rather than prescribing proteins for use by the cell. This of course makes sense when we consider the most common situation – normal cell differentiation. After all, all of our somatic cells contain a complete copy of our DNA beginning with fertilization and hence contain the DNA where-with-all to become any cell in the body. But becoming a multicellular organism is all about specialization, with cells differentiating themselves from one another to take on specific tasks such as making insulin in the pancreas or storing bits and pieces of navigational data and memories in the temporal lobe (*Gorman, 2013*). To specialize means shutting down unneeded genes, while activating others tasked with the very specific job at hand, such as making that insulin. Cell differentiation is therefore all about specialization and highly orchestrated sequences of gene activation and silencing, all without so much as changing one single base pair.

The subsequent differentiation of specific types of cells whether they be liver cells or tubular cells in the kidney must involve turning off genes which would otherwise turn cells into skin or nerve cells or a host of other cells, each with their special role to play and turning on genes which eventually turn cells into their fully differentiated form such as islet cells in the pancreas and turning off all those other genes linked with all those other highly specialized features characteristic of the other several hundred or so other cell types in the body.

Moving beyond natural cell differentiation is the issue of epigenetic change. For example, can methylation of DNA, unaccompanied by altering the nucleotide sequences of DNA, promote or suppress the activities of genes sufficiently to change the phenotype of a plant or animal? And if so, can those epigenetically induced influences on the gene expression be passed on to successive generations and become subject to natural selection? Environmental change has been shown to produce epigenetic changes such as methylation of DNA but whether and to what extent the ensuing

phenotypic changes can be passed on has been the subject of much debate (*Pennisi, 2013*). Fueling the debate is recent evidence that differences in the methylation patterns of DNA can alter the flowering times and heights of the *Arabidopsis thaliana* plant. Moreover these differences were inheritable over several generations, without significantly altering the nucleotide sequences of the plants DNA. Many epigenetic influences over gene expression are temporary, although they can be dramatic. For example exercise may turn off genes, which pose a threat of type II diabetes and affect fat metabolism (Reynolds, 2013).

More on Epigenetics: Genes and the Environment

Up until now we've looked at evolution through the lens of changes in the sequence of bases in DNA through mutations, duplication or gene swapping or any of a number of mechanisms for changing the nucleotide sequence. But that's only part of the story of how species might change in response to whatever challenges the environment throws their way. Less than twenty percent of human DNA codes for proteins – the rest – close to eighty percent, changes the “which and when” of how genes become activated or silenced. Switching on or off genes through the actions of intermediary molecules such as proteins, enzymes or RNA is one way to change species traits and behavior without changing base sequences.

After all this is precisely what happens during normal development. Every species – however complex – begins with one cell. That cell and every other cell to follow, carries the same full complement of genes, whether that cell be a nerve, liver or kidney cell. That's why we can sequence the entire genome from cells scraped from our cheeks or bone cells or any other somatic cell in the body in forensic cases or sequencing the genes of long dead relatives such as Neanderthals or Denisovans or long extinct animals. The key to differentiation is that whole suites of genes specific for any other type of cell are silenced or turned off and only those genes specific for the intended functions of the cell are 'active'.

But what if we could change that elaborately choreographed sequence of selection, activation or silencing of genes; yet leave the base sequences intact? We've just entered the world of epigenetics. Modifying the

activation and silencing of genes through the changes in the environment or even cultural and behavioral influences might change body shape (phenotype) and even function and thus introduce variation within a species without changing the DNA. RNA is yet another source of variation because like DNA, RNA can mutate and change the shape and functions of proteins – all without changing DNA. One example is the influence of the environment on the SRY gene on the Y-chromosome. The SRY gene dictates testosterone secretion in utero and hence the degree to which various male characteristics, that are testosterone dependent such as “muscle mass, aggression and genitalia development”, are expressed ([Quenqua, 2013](#)).

Epigenetic mechanisms are complex. For example in the nucleus, DNA is packaged in a three-dimensional structure, called chromatin, made up of nucleotides and proteins called histones. Histones possess amino acid “tails” which “stick out” and are subject to a vast array of chemical modifications, such as methylation, acetylation, or phosphorylation” specific combinations of which can alter the expression of genes ([Maya Kasowski et al. 2013](#), [Furey and Sethupathy, 2013](#) and [Epigenome Roadmap Nature 518, 19 February, Page 312](#)). These modified histone tails are highly variable in the human population, “heritable across generations” and capable of influencing traits such as height. It turns out however, that DNA variants may be responsible for some of those modifications in the tails of histones, which influence gene expression. So epigenetic phenomena may not be entirely free of influences from DNA: DNA may yet wag the “tail” of epigenetics after all.

The whole idea that environmental toxins might modify gene expression and that the latter changes might be passed on from generation to generation is highly controversial ([Kaiser, Science Vol 343 24 January 2014](#)). However the hypothesis offers an intriguing alternative to changing the DNA sequence, as the sole means of passing on inheritable traits.

Mass Extinctions and Evolution: Partners Shaping Species

The earth has undergone several major mass extinctions since the origins of life (see chapter 10) but we only know for certainty about five of those extinctions. The last occurred sixty-five million years ago and except for birds, did in the dinosaurs and opened the doors for mammals and eventually apes and humans to emerge. The idea that the earth suffered from mass extinctions in its past owes much to the life and work of *Jean Cuvier* (Kolbert, 2013 *Parts I and II in the New Yorker and The Sixth Extinction: An Unnatural History*, Henry Hold and Company New York, 2014). In his lifetime Cuvier studied a host of fossils – some quite spectacular such as the mastodon – a creature related to living elephants but clearly dating from an earlier time and for which no living representatives survived. Cuvier posited that the mastodon and a host of other reptiles, amphibians and various mammals had been lost in the wake of cataclysmic events in earth's past. His work preceded Darwin's *Origin of the Species* and although Darwin was not keen on Cuvier's posited mass extinctions and Cuvier for his part was not convinced by Darwin's hypothesis that natural selection was the sole engine which shaped the evolution of life, both their hypotheses stood up to the test of time and complement one another very well. The reason is that extinctions open up opportunities for other species to prosper by reducing competition and opening up sources for food; this despite the fact that the worst of these mass extinctions such as the one which occurred two-hundred and fifty million years ago, wiped out approximately ninety percent of the known species at the time. Major and more minor extinctions create opportunities for evolution to work and shape the surviving species, without which opportunities we would not be here! Species extinction and evolution are biology's equivalent to 'creative destruction', a term used by economists to refer the creation of new financial opportunities in the wake of recessions and depressions.

Evolution has not been the gradual incremental affair entirely guided by natural selection as Darwin suggested but characterized by long periods of relative stasis interrupted by relatively brief periods of explosive diversity. The latter usually followed some major natural disaster, followed in short order by the massive extinctions of many species, 'near death' experiences

for some survivors and the opening up of vast niches for other species to exploit and diversify (Leakey R, Lewin R (1996) *The Sixth Extinction: Patterns of Life and the Future of Humanity* Anchor Books A Division of Random House. Inc. New York, Page 266 and Kolbert E (2014) *The Sixth Extinction: An Unnatural History* Henry Hold and Company, New York).

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With shift of species to an urban environment, species reveal anatomical and behavioral changes, which sometimes reflect in changes in their genomes

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Analysis of more than 2000 species of birds reveal that most of the variation seen in modern birds reflect the development of a 'wide range of bill morphologies, with all kinds of extremes, dating back millions of years, and that widely separated species evolved similar repertoires for bill shape, suggesting convergent evolution in settling on similar solutions.

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Atlantic killifish evolved solutions to pollution, which enabled the species to survive in heavily polluted waters. The solutions at the genomic level were remarkably similar in different species and suggested that species with a high genetic diversity such as the killifish are best suited to adapt rapidly because they have a larger repertoire of genetic solutions on board for

solving the problems posed by the pollutants. The elected choice then rapidly spread through the population.

Rudiger Riesch and Martin Plath (2017) ***Evolution at the limits: Studies of fishes that inhabit toxic sulfide springs reveal mechanisms of natural selection***, Scientific American, April, Pages 55-59

The family of poeciliid fishes are remarkably capable of adapting successfully to waters highly polluted with hydrogen sulfide, a highly toxic compound which binds with oxygen in the environment, blocks the ability of hemoglobin to bind oxygen and freely penetrates the gills of fish. The fish adapted by developing larger mouths, including the lower lip and, increasing the size of their gills, all to increase the amount of oxygen they can extract close to the surface of the water. They also developed enhanced metabolic systems for detoxifying hydrogen sulfide. Similar adaptations were developed by different species of the poeciliid family of fishes in different environments. Taken together with the killifish experience, the two studies suggest that at least some fast-lived fish are capable over a few generations of adapting to some pollutants in the environment.

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Summary: Evolution and Genes

As I've pointed out human beings are prone to seeing ourselves at the top of the evolutionary heap and understandably assume that our genome would be remarkable, distinct and wholly more complex than others – even those closest to us on the evolutionary tree or bush. Surely we must have many more genes and much more sophisticated and complex at that, to account for the hierarchical position many religions put us in and certainly of which we have living proof in all that we have accomplished, compared to any other species, past or present.

However that is far from the case. At the molecular level we might be disappointed to learn that all that separates from Chimpanzees is little more than 1 percent of our genome. That's bad enough – but to find out that we share very close genetic facsimiles with nematodes and fruit flies seems over the top. There must be some mistake – perhaps many - in the counts and analysis of those large, substantial and very important complexes of genes which shape our very body plans for us to be so similar biologically with creatures we regularly quash and swat! Of course genes do differ from life form to life form but given the size of the whole genome its' surprisingly how little we differ from our ancestors hundreds of thousands of years ago and living life forms ranging from insects to mice or even plants.

Each of us then is the product of generations and generations of the mixing and matching of DNA; hundreds of thousands of years ago in the case of modern humans, several millions of years in the case of our African ancestors, fifty millions of years in the case of the earliest primates, to billions of years in the case of life itself. Look back far enough and its obvious that we are not only related to all life but that whatever the differences between the DNA of all living humans, whether Jews or Palestinians living in the middle East, the differences are trivial despite the yawning gulfs which separate their cultures, religions, wealth and opportunities – a fact we regularly lose sight of or having sight, choose to ignore.

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