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Jerry Bergman
University of Toledo Medical College

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Progressive Evolution or Degeneration?

Jerry Bergman, Ph. D., Adjunct Associate Professor, University of Toledo Medical College, Toledo, OH, 53502

Abstract

The published literature on the evidence for a mutational meltdown of life was reviewed. Although only a small percent of all mutations are detrimental enough to cause disease, the total number occurring in each generation is significant. It was once concluded that the vast majority of all mutations were neutral, but evidence now exists that indicates no or few mutations are truly neutral (though most mutations are near neutral). Clearly negative or harmful mutations are often effectively eliminated from the gene pool, and it is the "near-neutral" mutations that are causing mutational meltdown. Depending on the specific set of mutations, near-neutral mutations can accumulate only to a certain level before they are collectively lethal. It is concluded that the accumulation of mutations is a major problem for Darwinism because the large number of near-neutral mutations that are not readily selected out of the gene pool accumulate in each generation, eventually causing extinction. Mutations, rather then being the engine that drives evolution upward, are, instead, causing degeneration of the genome. Evolution is occurring, but going the wrong way, as predicted by the creation model. The reasons why mutations are accumulating in the genome are discussed in some detail.

Keywords

Mutations, Mutational meltdown, Code degeneration, Near neutral mutations, Species aging, Extinction

Introduction

Mutations are widely recognized as a major cause of disease. In a review of the mechanisms that drive genetic degeneration, Charlesworth and Charlesworth concluded that "most mutations with observable phenotypic effects are deleterious" (1998, p. 3). Estimates vary, but generally, around one new mutation occurs in "each round of cell division, even in cells with unimpaired DNA repair and in the absence of external mutagens" (Meisenberg & Simmons, 2006, p. 153). As a result, "every child is born with an estimated 100 to 200 new mutations that were not present in the parents" (Meisenberg & Simmons, 2006). Sanford (2005) puts the number of point mutations at about 200 and all types total at closer to 1,000.

Of these "an estimated one or two new mutations are 'mildly detrimental'," meaning they do not cause disease but can impair physiological functions to some degree, contributing to multifactorial disease (Meisenberg & Simmons, 2006, p. 153). The result is that on average every child has "new mutations on top of those inherited from their parents" causing an accumulation of mutations, increasing the mutational load and, eventually, causing genetic meltdown and extinction (Higgins & Lynch, 2001).

Potential evidence that the mutational genetic load in humans is increasing includes data recorded in the standard list of genetic diseases titled *Mendelian Inheritance in Man.* The first edition listed 1,487 genetic diseases, the current edition over 17,000 (McKusick, 1966, 1998). Several reasons exist for this dynamic increase, including the recent identification of existing genetic diseases, a larger human population that allows for more mutations of all types, and increased medical research in third-world nations. The increase also reflects, in part, a real increase in the total number of mutations in the human genome (Bataillon, 2000). This paper reviews the empirical evidence for this latter conclusion.

Near-Neutral Mutations

The core mechanism of evolution is the occurrence of mutations that are selected by natural selection—if the mutation confers a competitive advantage to the organism (Sanjuán, Moya, & Elena, 2004, p. 8396). Mutations that have "large deleterious effects" are often effectively selected out. Conversely, those "mutations with small effects are … less efficiently eliminated from the population" (Sanjuán, et al., 2004). As a result the "accumulation of weakly deleterious mutations" produces a "substantial … long-term rate of fitness decline" (Barton, Briggs, Eisen, Godstein, & Patel, 2007, p. 494). Most mutations were at one time thought to be neutral, that is, they have no adverse effects on the organism. As will be discussed, it is now known that many or most of these mutations are

not completely neutral, but are actually *near neutral* or "very slightly deleterious" for several reasons (Kondrashov, 1995). No mutation is really neutral if it causes a deviation from the amino acid set produced by the original gene because it always results in a change in the protein's original amino acid chain.

The neutral mutation concept was considered a "radical and highly controversial new view of mutations" when proposed in the 1960s by Motoo Kimura, (Lowenstein & Zihlman, 1998, p. 190). However, this view soon became widely accepted and was assumed to be valid for "the vast majority of mutations." The view that neutral mutations have "little or no effect" on an organism has been increasingly challenged in recent years. It is now known that even those mutations that have "little effect" on health can accumulate, causing major damage (Ohta, 1998; Sanford, 2005). Furthermore, evidence has accumulated that many putative neutral mutations are, in fact, not neutral, including the mutations in noncoding DNA that was once called junk DNA (Lowenstein & Zihlman, 1998). Among the studies that have found mutations in introns that cause disease (thus having a function) is included an intron in the calpain-10 gene that is associated with type II diabetes mellitus (Horikawa et al., 2000)

Research on near-neutral mutations, summarized by Lynch, Conery, and Bürger (1995b, p. 1067) has established that it is "now generally accepted that mildly deleterious mutations arise at a substantial rate in most higher organisms, probably as frequently as one per gamete". The number of known near-neutral mutations is enormous (Eyre-Walker, Keightley, Smith, & Gaffney, 2002). In human hemoglobin alone, close to 800 structural variants have been identified, most due to a single amino acid substitution and most of which are near neutral (Meisenberg & Simmons, 2006, p. 163). The number of existing mutations that do not cause protein structural variations are unknown, but the number is probably many times greater than those that cause structural changes. Also, known structural variations may be caused by more than one mutation.

Why Neutral Mutations are not Neutral

Some of the neutral mutations studied were those occurring in non-coding DNA, often called junk DNA. Coding DNA consists of only an estimated one to three percent of all DNA, or about one inch of the six feet of DNA in each human cell (International Human Genome Sequencing Consortium, 2004; Meisenberg & Simmons 2006). It is now widely acknowledged that many mutations in the alleged "junk" DNA are not neutral because much of it serves some function, including regulation, the assembly plans, and the control systems of the cell and the entire organism. Evidence for the importance of noncoding DNA is that it is highly conserved, indicating that much—or most of it—is functional (Gibbs, 2003).

It was once thought that these mutations were largely neutral. For example, components of the blood clotting system called fibrinopeptides function as spacers to keep the sticky molecular surfaces apart until a clot is required. The spacers are then removed and recycled, allowing the active protein form to exist. Though they function only as spacers, their specific composition can affect the clotting system effectiveness. Experimental evidence has found that the former conclusion that almost any amino acid will perform a spacer function equally well is incorrect for several reasons, including that certain amino acids can interfere with proper folding (Minshull, Ness, Gustafsson, & Govindarajan, 2005). Mildly deleterious mutations in mitochondrial and chloroplast genomes, and also in transfer RNAs (tRNAs) and ribosomal RNA, gradually accumulate in the genome, and both contribute to mutational meltdown (Lynch & Blanchard, 1998, p. 29). This accumulation has been documented in a wide variety of life-forms including animals, plants, fungi, and prokaryotes (Lynch & Blanchard, 1998).

Synonymous Codons

Another major mutation group once felt to be neutral is a class called "synonymous" mutations. One example is the putative neutral mutation that changes a codon, such as UCU which codes for serine, into a new codon, including UCC, UCA, and UCG, each of which are also translated into serine. The translation occurs because of the so-called wobble effect caused by the common third base redundancy. As many as six codons will produce the same amino acid, and most amino acids can be coded by at least three synonymous codons.

The new wobble codon is rarely lethal, but it *is* often slightly less effective. One reason why it is less effective is the fact that tRNA production levels often correlate with the original codon requirements, and a change causes tRNA supply imbalance problems.If a cell rarely uses a specific codon, it produces lower levels of the tRNA needed for that codon (Clark & Russell, 1999, p. 220). For this reason, a strong positive correlation exists between codon usage levels and tRNA content in a given organism (Ikemura, 1985). Consequently, athough the protein produced does not change, cellular efficiency does. This problem, called *codon usage bias*, in which a certain codon from the functional set is favored, is clear evidence for non-neutrality of synonymous substitutions. Another finding is that synonymous substitutions can change the structure and function of the final protein (Minshull et al., 2005).

Further evidence that codon mutations are not neutral includes the fact that genes with high

codon usage bias "have lower rates of synonymous substitution between species then do genes with low codon usage bias" (Powell & Moriyama, 1997, p. 7785). An example is lysine, which can be coded by AAA or AAG. In *E Coli*, the AAA codon is used 75 percent of the time, and in rhodobacteria the opposite is true—AAG is used 75% of the time. If a gene with a large number of AAA codons for lysine is transfected into a cell that almost never uses the AAA codon, its tRNA is then in such short supply that protein synthesis for that gene will slow down significantly (Clark & Russell, 1999, p. 220). This indicates that both tRNA regulation and the genetic code must have been in place simultaneously in order for the cell to function.

Another example of non-neutral mutations are the six different codon triplets that code for leucine in *E. coli,* 49 percent of which are CTG; in yeast 10 percent of leucines use this code compared to 44 percent in the fruit fly and 41 percent in humans. This effect is another example of codon usage bias where a cell uses a particular codon only rarely: it produces lower levels of tRNA for that codon. In almost every organism studied so far, codon usage bias exists for a particular codon for each amino acid (Eyre-Walker et al., 2002; Ikemura, 1985; Moriyama & Hartl, 1993).

Codon usage bias, which is one example of non-neutral mutations that can have long-term deleterious effects, does not conform to neo-Darwinian predictions. If certain codons from the functional set were not favored, that is, if the proportion of codon usage were the same for all bacteria (which it is not), this could be seen as evidence for evolution. But we do not see evidence of a neo-Darwinian relationship in this pattern; in fact, we often find that two organisms judged close by evolutionary phylogeny do *not* have a similar coding usage bias compared with those judged phylogenetically distant.

Neo-Darwinists argue that the codon evolved first, and the tRNA regulation system evolved later. But it could just as well be argued that tRNA regulation developed first, and this influenced the protein codon selection so that more of certain tRNAs influenced the codon used by that tRNA to become more common. Nonetheless, no evidence exists that a change has occurred historically in either codon frequencies or in tRNA regulation.

The codon usage bias level varies among organisms. For some amino acids in some organisms, its effect is large enough to impact the animal's survival. Research indicates that, with the exception of aspartic acid, most amino acids contribute significantly, and about equally, to the codon usage bias effect (Powell & Moriyama, 1997, p. 7784). As these near-neutral mutations accumulate, overall cellular efficiency slowly declines, resulting in an overall negative effect on the fitness of an organism.

Founder Mutations

Other evidence for a mutational meltdown includes founder mutations (Drayna, 2005). Founder mutations are disease-causing mutations that are not effectively eliminated by natural selection. As a result, the mutation persists in the population and can even become widespread, such as the mutation responsible for sickle cell anemia (Biswas, 2006). The ancestor that suffered the first mutation, introducing the mutation into the gene pool, is known as the "founder." Although often lost in history, some founders have been traced to a general geographical location. The most studied founder mutations have been traced to specific populations such as the Amish, Jews, Dutch, and Gypsies (Ben-Yosef & Friedman, 2003; Jääskeläinen et al., 2004; Levine et al., 2003; Navarro & Teijeira, 2003; Zeegers, van Poppel, Vlietinck, Spruijt, & Ostrer, 2004).

Documented cases of founder mutations include certain forms of holocarboxylase synthase deficiency disease (Suzuki, Yang, Aoki, Kure, & Matsubara, 2005), mucolipidosis type IV disease (Bach, 2005), hereditary nonpolyposis colorectal cancer (Guillem, 2004), early-onset Parkinson's disease (Hedrich et al., 2004); familial Mediterranean fever (Touitou, 2001) of which five founder mutations account for all 74 cases studied; Hermansky-Pudlak Syndrome (Huizing & Gahl, 2002); BRCA1 and 2 (Liede & Narod, 2002; Lonning et al., 2001; Rubinstein, 2004;) hypertrophic cardiomyopathy (Jääskeläinen et al., 2006), hereditary paraganglioma (Baysal, 2004), Crigler-Najjar Syndrome, and canavan disease (Surendran, et al., 2003). Yet another is factor V Leiden, an important risk factor in various thromboembolism diseases (Rees, Cox, & Clegg, 1995).

The study of founder mutations has proven important in a variety of genetic studies (Rosenberg, 2003). Founder mutations are most likely to persist in the population if the mutation is recessive, especially if a recessive copy can confer some advantage to the carrier, such as is the case with sickle cell anemia and cystic fibrosis disease, in which a CTT deletion accounts for virtually all cases of the disease in humans.

Several founder mutations can contribute to one disease. For example, at least five different haplotypes exist for sickle cell anemia, lending strong evidence to the hypothesis that at least five founders exist (Allison, 2002, p. 285). Another good example is hemochromatosis, caused by a mutation on the HFE gene on human chromosome six that disrupts the iron regulation system. This causes excessive iron absorption, eventually leading to organ damage and even death if not treated. The mutation evidently originated in central Europe about 65 generations ago, and is now present in at least one of the two HFE genes in an estimated 22 million Americans.

Many founder mutations persist because they do not affect the victim until after childbearing years. An example is the trinucleotide repeat disorder called Huntington's Disease, a condition that now affects many thousands of persons. Traced back to at least 1630, it is now known, thanks to the work of Dr. Nancy Wexler, that the gene was brought by a few individuals to both North and South America. Because it is a dominant gene, on average it affects about half of all offspring of couples, of which at least one partner is a carrier. This neurodegenerative disease causes gradual dementia, uncontrolled movements, and eventually death (Duyao et al., 1993).

The symptoms of Huntington's Disease usually do not show up until after the fourth or fifth decade of life, after normal reproductive years are past. Many carriers, due to genetic testing, are now aware they have the gene in their family. Some victims, knowing that about half of their children will develop the lethal disease, still elect to have children. Founder mutations are significant examples of deleterious mutations because before these mutations entered the human genome, the diseases they cause did not exist. As founder mutations accumulate in a species, the accumulation contributes to the degeneration of the genome, especially a problem for those species with small population sizes (Keightley & Eyre-Walker, 2000; Sanford, 2005).

Genetic Drift and Interbreeding Depression

Another problem contributing to genetic meltdown is random genetic drift that allows near-neutral mutations to spread to an entire population, increasing the probability of the "extinction of the whole population, or the degeneration of non-recombining portions of the genome" (Charlesworth & Charlesworth, 1998, p. 3). This is especially problematic in both small populations andpopulations that would typically outbreed but do not for forced or self-imposed reasons, such as the Amish, a religious group that is known to suffer from a large mutational load. As a result from founder mutations, the Amish "experience an inordinately high incidence of certain genetic-based diseases," many of which are fatal or disabling (Shachtman, 2006, p. 24). An example is Crigler-Najjar syndrome, a genetic disorder that is caused by high levels of bilirubin, which produces severe jaundice, resulting in brain damage and death. The specific cause is a damaged liver enzyme that is part of the metabolic breakdown pathway of bilirubin. Worldwide, fully 20% of all cases are found in the tiny Amish population (Morton, et al., 2003).

Selection reduces their mutational load—Amish families often lose one or more children to genetic diseases—yet the mutational load keeps increasing. Often genetic diseases, such as many metabolic disorders, can be treated, allowing those so afflicted to reach the age of sexual maturity and pass the mutations on to their offspring. In 1988, three dozen major genetic diseases were identified among the Amish; now fully five dozen are known (Shachtman, 2006, p. 28).

Are Polymorphisms Just Variety?

Another example of deleterious mutations is certain genes that were all once assumed to be an example of normal variety. Some or possibly many of these genes called polymorphisms (about one percent of the genome) may be near neutral or even harmful mutations and not just normal variations (Nachman, 1998, p. 61). As more polymorphisms are researched, it has been found that some examples once regarded as normal variations are mildly deleterious. For example, blue-eyed and fair-skinned persons are significantly more prone to skin cancer, even in environments where it was assumed that these traits were important in survival, such as locations where an increased vitamin D production is beneficial. Blue eyes are caused by lack of pigmentation on the iris, and blue-eyed persons are more prone to certain eye problems, such as difficulty working in bright environments, retinal pigment epithelial depigmentation, and other vision problems (Acosta, Alfaro, Borras, Belmonte, & Gallar, 2006; Singh, Rennie, Seregard, Giblin, & McKenzie, 2004; Tomany, Klein, & Klein, 2003).

Redundancy in Life

Yet another reason why most mutations are rarely (if ever) neutral is because of the redundant systems in most life-forms. Survival, at least to the point of reproduction (the key to natural selection), is rarely affected in cases where a backup organ exists (the phenomena of organ redundancy). Humans can normally survive quite well without tonsils, adenoids, spleen, appendix, one kidney, or a lobe of the liver, allowing mutations that affect these organs to be passed on to one's offspring and become part of the human genome. If a mutation damages an organ, redundancy allows a considerable number of mutations to accumulate that will only be weakly selected against.

Another redundancy factor is the fact that all sexually reproducing organisms possess two copies of most genes. If one gene mutates, the other allele on the sister chromosome can produce the correctly folded protein. The single copy condition allows mutations to accumulate because the mutation that is not effectively selected out if the *other* gene can still perform the sister gene's function. This redundancy allows damaged genes to accumulate in the genome, contributing to the mutational meltdown problem. If humans were haploid, a normal gene mate would

not be present to compensate for a damaged gene, and the affected person would be more likely to die early without passing genes on to offspring. As these near-neutral mutations accumulate, the strain on the system increases.

Although redundancy often allows survival, heterogeneous mutations can affect dosage levels, requiring compensation. Recessive mutations may also damage the working unit. For example, the p53 transcription factor is a tetrad of four p53 proteins, and if even a single protein in the tetrad is damaged, the transcription factor will not function. Despite this, recessive germline p53 mutations are often not lethal until after having children. Familial p53 mutation patients (Li-Fraumeni Syndrome) usually die of cancer but can live into, and even past, childbearing age, allowing them to pass the mutation on to their offspring (Vogelstein & Kinzler, 1998, pp. 398–399). Redundancy is not always an advantage, such as is the case with triplet repeat expansion disorders and possibly some co-dominance genetic conditions.

The fact that most known human genetic disorders are recessive explains how the mutations are passed on to the next generation. Some well-known examples include cystic fibrosis, sickle cell anemia, and Tay-Sachs disease. Since a person must have both genes in order to have the disease, only a small portion of the affected population will die from the disease, allowing others with the mutation to pass it on. Evidence for this conclusion is the high frequency of many recessive mutations in the population. For example, among Greeks, factor V Leiden is present in around 7% of the population (Rees, Cox, & Clegg. 1995, p. 1133). Cystic fibrosis strikes thousands each year; about one in every 20 Caucasian Americans (a total of 12 million persons) is a carrier of an abnormal CF gene; most are unaware that they are carriers. Among blacks, about 7.8% are sickle cell anemia carriers, and about 0.15% actually have sickle cell disease (data from NIH Publication No. 95-3650).

Lethal Mutations that have Selective Advantages

Lethal or deleterious mutations are actually selected in certain circumstances. The most common examples actually encourage the spread of lethal mutations, contributing to the accumulation of mutations in the genome. The classic example of a generally harmful mutation that can have a beneficial effect in specific situations is sickle cell anemia (Ridley, 1996, p. 118). The homozygous form is lethal, causing approximately 100,000 deaths annually, but the heterozygous form provides a survival advantage where malaria is common. The heterozygote form, although it causes anemia, does not result in a level of sickling that significantly affects blood circulation. For this reason the mutation is said to be latent.

If the malaria parasite *Plasmodium falcipurum* infects an erythrocyte, the victim with a heterozygote mutant form is more likely to survive. It has been well documented that persons with one damaged gene survive better in areas of the world where the malaria parasite is common. The parasite feeds on the hemoglobin molecule, causing the oxygen concentration in the cell to decline, resulting in sickling of the infected cell. Sickling in turn causes that cell (and the malaria parasite in it) to be destroyed by the spleen (Ridley, 1996, p. 118). Many other examples of heterozygous mutations exist that provide a selective advantage in limited conditions but would be selected out in most circumstances. Examples include some thalassemia herterozygotes, which provides an advantage against malerial parasites as does the sickle cell allele; the CCR5 deletion, which gives some protection from AIDS; and glucose-6-phosphate dehydrogenase variant (G6PD-Mediterranean). G6PD deficiency, a condition characterized by severe enzyme deficiency, but confers some resistance to falciparum malaria. (Beutler, 1996; Kurdi-Haidar et al,1990).

Methylation of DNA

Methylation of DNA is a major means of controlling gene expression. Methylation is used for significant genetic regulation to achieve cellular differentiation and dosage compensation, such as lyonization in females, which silences one X chromosome. Specific methylation sites are a heritable phenomenon that selectively reduces gene expression by increasing the binding of repressors. Alterations of methylation sites can be passed on to future generations and therefore contribute to the degeneration of the genome.

Methylation is also a major means of causing gene imprinting to achieve sexual differentiation by turning off one set of somatic genes in males and another set in females (Baysal, 2004). Changes in methylation can adversely affect all of these critical genetic functions. Disruption of methylation is not effectively repaired, allowing loss of this epigenetic means of control to accumulate and, in time, contributing to genetic meltdown.

CpG islands are a region of 1–2 kb sequences containing a high density of methylated cytosine residues. In plants, fungi, and animals, it is the cytosines are usually methylated, but in bacteria the adenosines are normally methylated (Turner, 2007, p. 214). In plants, the methylated sequence is ... CpNpGp ... where N can be any base. CpG islands are a site of high mutational frequency because spontaneous deamination of the methylated cytosine 5-methylcytosine results in thymine, which is not recognized by DNA repair enzymes and unrepaired, resulting in genomic degradation (Coulondre, Miller,

Farabaugh, & Gilbert, 1978). Approximately 5% of vertebrate DNAs consist of 5-methylcytosines, and with time more and more conversion of C to T occurs by this process.

Modern Medicine

Modern medicine can contribute to genetic degeneration because it may allow children that have lethal mutations to live long enough to reproduce, increasing the human mutational load. The mutational load is thus reduced by natural selection and increased by modern medicine. Historically in many societies as many as half of all children died before they were old enough to reproduce. Those who died had, on average, not only more detrimental mutations, but also more near-neutral, detrimental mutations than those who survived. Medicine, antibiotics, and better nutrition and sanitation have reduced this death rate significantly (Meisenberg & Simmons, 2006, p. 153). Darwin recognized this concern and for this reason opposed vaccinating because the procedure

> has preserved thousands, who from a weak constitution would formerly have succumbed .... Thus the weak members of civilized society propagate their kind ... this must be highly injurious to the race of man. It is surprising how soon a want of care, or care wrongly directed, leads to the degeneration of the domestic race ... we must bear without complaining the undoubtedly bad effects of the weak surviving and propagating their kind (1871, pp. 168–169).

Although Darwin's example is incorrect because infectious disease effects largely those with weak immune systems or those who lack resistance), his point is valid with many diseases. This point does not condemn the use of modern medicine as Darwin did, but recognizes the fact that an unfortunate side effect is that medicine has reduced enormously the infant mortality rate, allowing persons with detrimental mutations to have offspring and pass them on to future generations. Lynch, et al., opines that with animal life the problem of deleterious mutation accumulation may be exacerbated in endangered species that are confined to breeding facilities. Since captive environments are usually quite benign (including services from dietitians, veterinarians, artificial inseminators, etc.), a real possibility exists that mutations that are significantly deleterious in nature are rendered nearly neutral. If that were the case, regardless of the population size, deleterious mutations would accumulate at nearly the neutral rate, $\mu/2$ per generation, although their effects would go undetected until the population was reintroduced into the wild. At that point, the population might no longer be capable of sustaining itself without continued human intervention (Lynch, 1996, p. 489).

Mutations Compensated for by Dietary Alterations

An important class of mutations are those that damage an enzyme, a metabolic pathway, or a mediated transport system that moves materials across a cell membrane. Many of these mutations cause diseases that can be successfully treated by dietary changes, allowing the patient to survive and pass the mutation on to their progeny. The most well-known example is phenylketonuria (PKU), a metabolic disorder that results in the buildup of toxic byproducts from the defective breakdown of phenylalanine. PKU is successfully treated by a rigid dietary restriction of phenylalanine, an essential amino acid (Meisenberg & Simmons, 2006, p. 494).

Newborn screening for PKU is mandatory in many countries. The disease, which, depending on the mutations involved, normally causes severe retardation, seizures, spasticity and other neurological problems that prevent the victim from passing the mutation on to offspring. However, by following dietary restrictions, PKU patients now develop normally and can freely pass the mutation on to their offspring (Meisenberg & Simmons, 2006, p. 494). Although phenylalanine is nutritionally essential in small amounts, it can be greatly reduced by such dietary restrictions such as avoiding the artificial sweetener aspartame and other foods and condiments that contain large amounts of phenylalanine without adverse health effects. Again, the human and proper response has unintended undesirable side effects.

Some other examples of the many known metabolic diseases caused by mutations include trypsinogen deficiency treated by dietary supplementation of protein hydrolysate and celiac disease treated by a gluten-free diet (Frezal & Rey, 1970, pp. 287–288). Gluten, found in wheat, rye, and barley, can be avoided by not eating foods containing these grains. Other examples include milk protein intolerance treated by complete avoidance of cow's milk. Depending on the specific mutation involved, the problem is often an inability to process casein and lacto-serum proteins. Another example is sucrose and isomaltose intolerance, usually treated simply by removal of sucrose and starch from the diet. Most of these diseases are lethal if not treated, and the cause of most of them was unknown until recently (Frezal & Rey, 1970, p. 306).

Mobile Elements Damage the Genome

Much of our genome is currently believed to contain what is often, and probably incorrectly, called "parasitic DNA," which are a result of what is known as jumping genes or—more formally—mobile elements. How many of the mobile elements cause damage is not known, but the fact that the DNA in our 46

chromosomes, some conclude, contains an estimated three million mobile DNA segments indicates the damage may not be minor. This mobile DNA includes retroviruses—a type of retrotransposon similar to the AIDS virus. Other examples include Long Interspersed Elements (LINES) or Short Interspersed Elements (SINES). Research evidence indicates that some retrovirus LINES and SINES have vigorously colonized the DNA of mammals. LINES use two genes of their own, and SINES, which do not have genes to splice themselves into the genome, must instead hijack the enzymes of other putative parasites in order to copy and paste themselves into new DNA sites (Kazazian, 2004, p. 1626). Even if most all of the parasitic DNA is found to have a use, the small amount of misplaced or actual parasite DNA could do a significant amount of damage.

These mobile elements normally insert themselves into DNA at selective sites but sometimes insert themselves at other sites, disrupting a gene and causing a mutation. An estimated one in every 200 babies has inherited a new damaging putative parasitic element, and one in every 1,000 patients has a new genetic disease as a result of a misdirected mobile element that has disrupted an important gene (Ostertag & Kazazian, 2001; Deninger & Batzer, 1999; Ostertag, Goodier, Zhang, & Kazazian, 2003). Assuming that these estimates are correct, this damage will result in a significant increase in the mutation load.

Some cancer-causing viruses also splice themselves at random sites into human DNA. When a particular viral DNA section is found at the same position in the DNA in every cell in a cancer tumor, all of those cells are believed to be descended from the cell in which the unique viral insertion occurred—the founder mutation (Ng, Guan, Poon, Fan, & Lee, 2003; Tsukaski, Koeffler, & Tomonaga, 2000). Some common examples include papilloma viruses, hepatitis, and some forms of leukemia. Founder mutations caused by mobile element insertion errors are not reversed by any known dedicated mechanism, and, unless lethal before reproduction, they accumulate in the genome, contributing to genetic degeneration.

Another example is the Alu elements that are amplified by retrotransposition, an RNA-dependent mechanism. Although they are believed to be functional in humans, they continue to accumulate at the rate of one insertion for every 200 new births (Deininger & Batzer, 1999, p. 183). At least 16 new diseases have been identified as being caused by new Alu elements, including hemophilia, neurofibromatosis, chlorinesterase deficiency, glycerol kinase deficiency and several cancers (Deininger & Batzer, 1999, p. 184). Alu elements alone may cause as much as 0.4% of human genetic disease. Another major mobile unit of DNA is the L1 element, which is much longer then Alu elements. L1 elements can also supply the needed components for Alu retrotransposition.

Tandem Repeat Expansion Disorders

Many genes consist of repeats of sets of three or more bases called tandem repeat bases. They tend to be mutational hot spots (Sutherland & Richards, 1995). The "length of tandem repeats is prone to change through mutation," and in each generation they can increase, a problem called stuttering, eventually causing disease because the expanded protein forms abnormal complexes with other proteins (Meisenberg & Simmons, 2006, p. 127). For example, Huntington's disease is caused by an expansion of the CAG trinucleotide repeat. CAG is normally repeated from 6–34 times and causes disease if it expands beyond 36 repeats. The repeat often expands in each generation, and the more it expands, the earlier the onset of the disease. Other common examples of tandem repeat disorders are fragile X syndrome, Friedreich ataxia, and myotonic dystrophy (Campuzano, et al. 1996; Hagerman & Cronister, 1996; Mahadevan, M., et al. 1992)

Pseudogenes

Evidence indicates that many pseudogenes are damaged genes. For example, most animals (except humans, apes, monkeys, fruit bats, several species of fish, and guinea pigs) can manufacture an enzyme that is critically important in vitamin C production. The L-gulono-gamma-lactone enzyme catalyzes the last step of vitamin C synthesis (Nishikimi, Fukuyama, Minoshima, Shimizu, & Yagi, 1994). Lack of about 60 mg of vitamin C daily in humans leads to serious health problems, including scurvy, which has historically been a major killer.

Humans possess all of the enzymes required to manufacture vitamin C except L-gulono-gamma-lactone (Inai, Ohta, & Nishikimi, 2003). A pseudogene that is about 70% similar to the functional gene exists that appears to be a damaged L-gulono-gamma-lactone gene. Specifically, it lacks critical control sequences, such as the promoter, required to transcribe the gene (Zhang, Harrison, Liu, & Gerstein, 2003). The human pseudogene has four of the 12 exons of a similar functional L-gulono-gamma-lactone gene in the rat. These four rat exon sequences have 70–80% homology to the human pseudogene. If this pseudogene is, in fact, a damaged functional gene, its loss has resulted in an enormous number of human deaths. Of the thousands of pseudogenes believed to exist, no doubt, some do have a function, such as for genomic regulation, but it is likely that some are damaged functional genes. No one knows how common pseudogenes are, and estimates vary

widely, but they are believed to be very common. Gerstein and Zheng claim that they "litter our chromosomes" (2006, p. 49). This is evidence for a genetic meltdown instead of the genetic build-up that is required by evolution.

Genetic Meltdown Evidence

These few examples illustrate why the accumulation of near-neutral mutations contributes to the "mutational meltdown" problem, eventually causing extinction (Lynch, Conery, & Bürger, 1995a, b; Eyre-Walker & Keightley). As early as 1964 Muller proposed that even very large populations of asexual organisms would inevitably accumulate deleterious mutations (Barton, Briggs, Eisen, Goldstein, & Patel, 2007, p. 681). Muller concluded that the result would be a gradual ratchet-like increase in mutations, eventually causing the extinction of the organism, an effect called "Muller's ratchet" (Muller, 1964).

Muller concluded that the accumulation of deleterious mutations eventually results in the extinction of even the most fit organisms. This problem is most serious in asexual organisms and is exacerbated by both a high mutation rate and small populations. The reason is "in the absence of sex, deleterious alleles accumulate" because sex produces recombination as a result of genes from each parent. Furthermore, all

> populations must continually eliminate deleterious mutations if they are to survive. This elimination is much more efficient if there is recombination …. [T]he primary function of sex and recombination may be to prevent the fatal accumulation of mutations. Because all organisms suffer a mutation load, this is an attractive general explanation for the prevalence of sex and one that has received much attention in recent years. Sexual reproduction can reduce the mutation load …. If mutation is always from good alleles to bad (a reasonable approximation) then the fitness of an asexual population is reduced … if there is negative epistasis, so that the effect of each additional mutation becomes more severe as the number of mutations increases, then negative linkage disrequilibria will be generated. Recombination breaks these up and, by doing so, can substantially reduce the mutation load. This gives a population-level advantage for sexuals over asexuals (Barton, et al., 2007, p. 680).

In a typical study of the mutational load problem that examined 1,700 generations, Andersson and Hughes found 1% of the 444 lineages of a DNA based microbe studied "had suffered an obvious loss of fitness" (1996, p. 906; Nachman & Crowell, 2000). The researchers concluded that genetic mechanisms in asexual populations, such as back mutations or compensatory mutations, "cannot compensate for the accumulation of deleterious mutations" (1996, p. 906). Lynch et al. concluded that, although it is "widely acknowledged that the gradual accumulation of mildly deleterious mutations is an important source of extinction for asexual populations," evidence now exists to support the conclusion that the gradual accumulation of near-neutral mutations causes the same result in sexual populations (1995b, p. 1067). They add that computer simulations supported by analytical approximations

> indicate that mutation accumulation in small, random-mating monoecious populations can lead to mean extinction times less than a few hundred to a few thousand generations …. Under all mating systems, the mean time to extinction increases relatively slowly with the logarithm of fecundity, and mutations with intermediate effects (similar to those observed empirically) cause the greatest risk of extinction" (Lynch et al., 1995a, p. 1067).

A study of the mechanisms that purged fixated deleterious genes noted that "a large fraction of mutations" are "unconditionally deleterious" (Lynch, 1996, p. 483). Lynch added that the "accumulation of deleterious mutations" influences the mean fitness and extinction risk, especially of small populations. He concludes that the "worst-case scenario is realized when the size of the founder population is so small that random genetic drift completely overwhelms the power of natural selection" (1996, p. 486). Slightly deleterious and near-neutral mutations also accumulate in mitochondrial DNA. Evidence now exists that "many mitochondrial amino acid polymorphisms are deleterious" (Nachman, 1998, p. 67). Random factors and genetic drift are also important. Barton et al., conclude

> any kind of selection causes random fluctuations at linked loci, which may by chance fix deleterious mutations. This effect is especially severe in strictly asexual populations … even in a very large asexual population, deleterious mutations must accumulate [and even] … the fittest genotype can be lost by chance, and once lost, it can never be recovered …. [T]he whole population must trace its ancestry back to the fittest class …. Once the fittest class is lost, the process begins again, but with all individuals carrying one extra mutation. Even if the population size is in the millions, weakly selected mutants will still accumulate (Barton et al., 2007, p. 687).

Mutation Rates

To assess the contribution of near-neutral mutations to the mutational meltdown problem, understanding the rate of mutations is critical (Crow, 1997; Neel et. al., 1986). The rate that mutations are expressed depends on a wide variety of factors, and this is one reason why the mutation rate can only be estimated (Kondrashov, 1998). For example, the mutational expression rate is

higher in cases of self-fertilization and inbreeding, but lowed when synergistic epistasis. is involved. Epistasis refers to the interaction between genes: *synergistic* is a positive interaction (higher expression of the trait), *antagonistic* a negative interaction (lower expression of the trait). Charlesworth and Charlesworth conclude that the mutation rate is so high that highly inbreeding species are expected to have a short existence (1998, p. 15).

Andersson and Hughes found a deleterious mutation rate of 0.3 to 1.5 mutations per billion base pairs per generation in *Salmonella typhimurium*, which they characterized as having a "typical genomic mutation rate" for bacteria (1996, p. 906). Work on *Drosophila* suggests a rate of 0.5 mutations per generation that causes a reduction of fitness by one to two percent per generation (Charlesworth & Charlesworth, 1998, p. 15). This number is significant because bacteria and fruit fly generations consist of a matter of minutes or days. In the laboratory "rates of spontaneous mutation per genome as measured in the laboratory are remarkably similar within broad groups of organisms, but differ strikingly among groups" (Drake, Charlesworth, Charlesworth, & Crow 1998, p. 1667). They estimated that in microbes the rate is 1/300 per genome per replication and in higher eukaryotes from 0.1 to 100 per genome per sexual generation. For mammals the mutational meltdown would be expected to take thousands of years.

More recent research that obtained the first direct estimate of mutation rates in complex organisms found evidence that mutation rates are about 100 times higher than previous estimates (Denver, Morris, Lynch, Vassilieva, & Thomas, 2000). Most of these studies ignored what were considered neutral mutations. The current estimate for all mutations is approximately one unrepaired mutation occurs for every one hundred million nucleotides copied each generation. With three billion base pairs in humans this equals a minimum of 30 new mutations per individual (Behe, 2007, p. 11). A literature review by Sanford (2005) found that the number of mutations is even higher. Barton et al. concluded that the total genome-wide mutation number that changes amino acid sequences is about 0.9 per haploid genome per generation. If even a small proportion of these were only mildly deleterious, a significant number could accumulate. Although the "effect of each mutation would be small, the long-term rate of fitness decline could be substantial" (Barton et al., 2007, p. 494).

These studies indicate much work is needed in this area to understand different mutation rates found, which depend on the organism, where the mutation occurs in the gnome, the effectiveness of the repair system, and the effectiveness of natural selection to remove mutated organisms from the gene pool. Nonetheless, the rate is so significant that numerous researchers have explored the obvious question: why have we not seen a genetic meltdown in all life by now (Kondrashov, 1995)? A common answer is that natural and sexual selection both work to slow down, but not stop, the mutational load increase (Andersson & Hughes, 1996, p. 907). The genetic meltdown is proceeding forward, although far less rapidly then it would if selection and sexual reproduction did not exist. Meisenberg and Simmons note that the

> mutational load is kept in check by natural selection. In most traditional societies, almost half of all children used to die before they had a chance to reproduce. Investigators can only guess that those who died had, on average, more "mildly detrimental" mutations than those who survived (2006, p. 153).

Mutational rates are misleading because the 45,000–50,000 detected coding regions in humans produce over 100,000 different proteins due to alternative splicing (Bertone, et al, 2004). As a result, one mutation may result in several defective proteins. Furthermore, "it is likely that nearly all human genes are capable of causing disease if they are altered" in ways that produce defective proteins that affect their function (2002, p. 1514). The ENCODE project found that the same is true of mutations in the large number of regulatory DNA. The near-neutral mutations, and those that allow the afflicted to survive, can add to the total genetic load of near-neutral and deleterious mutations. Another factor is over one dozen mutation repair mechanisms are known to exist, and, no doubt, more await discovery. Research on persons exposed to radiation indicates that after several generations, the repair system and natural selection may reduce the mutation load. This effect tends to maintain stasis, an effect that opposes evolution.

Summary

The evidence shows that evolution by means of mutations, under the influence of natural selection, is real but, in the long run, results in degeneration of genomic information—not in an improvement as required by orthodox evolution. As Lynch concludes, assuming back mutations are rare and discounting the effect of recombination and segregation, a parent "can never produce an offspring with fewer deleterious mutations then it carries itself" (1994, p. 1067). The mutational load will, in general, increase with each generation, and since most all (if not all) mutations are either near-neutral or deleterious, the result will be genetic deterioration, eventually leading to genetic meltdown and extinction. Direct experimental genetic evidence of this conclusion has been found in laboratory research with *Saccharomyces cerevisiae* populations (Zeyl, Mizesko, Arjan, & De Visser, 2001). Both near-neutral and detrimental mutations were

evaluated, focusing on the reasons why detrimental mutations were not eliminated by natural selection.

Although only a small portion of all mutations in eukaryotes is detrimental enough to directly affect survival, the total number occurring in each generation is significant (Kondrashov, 2002). It was once concluded that the vast majority of all mutations were neutral, but evidence now exists indicating that few mutations are truly neutral: most mutations are near neutral (Sanford, 2005, p. 72). Clearly harmful mutations are often effectively eliminated from the gene pool, and it is the "near-neutral" mutations that are causing concerns about mutational meltdown of life because they accumulate in the genome. The most common example is aging, which is a result of an accumulation of mutations, but evidence now exists that the genome itself is also aging (Sanford, 2005).

This review confirmed Sanjuán's conclusion that "mutations typically lead to reduced fitness," but fortunately, many mutations are "removed by purifying selection" (Sanjuán et al., 2004, p. 8396). The problem is the near-neutral mutations—those that are not lethal and, for this reason, are allowed to accumulate in the gene pool. As Lynch concludes

> what little we know about deleterious mutations raises the real concern that their recurrent introduction can threaten the persistence of even moderately large populations over time scales of several dozens of generations (1996, p. 489).

This is because many factors intersect. For example, *osteogenesis imperfecta*, or brittle bone disease, is caused by mutations in the genes that make 1 procollagen, both COL1A1 and COL1A2 genes. Although *osteogenesis imperfecta* is, in the vast majority of cases, inherited in a dominant fashion, its penetrance is variable, meaning the clinical characteristics and severity vary greatly (Plotkin, 2007). Most victims survive to adulthood and have families, and many patients with mild forms may not even be aware of their condition. Thus, the mutation is commonly passed on and has become a part of the human genome load. The disease can effect several organs and even whole organ systems, disproportionately contributing to the human mutational breakdown problem (Plotkin, 2007). New mutations introducing the disease in new genetic lineages are fairly common, resulting in an increase in the rate of *osteogenesis imperfecta* in the population in addition to inherited cases.

Conclusions

The main mechanism contributing to this meltdown is the "recurrent introduction of new deleterious mutations in each generation" (Lynch & Blanchard, 1998, p. 29). The accumulation of mutations is a major problem for Darwinism, mainly because of the large number of near-neutral mutations that are not readily selected out of the gene pool. These accumulate in each generation, eventually causing extinction. It was found that certain clearly negative mutations are not selected out from the gene pool for at least a dozen reasons, and as a result they accumulate in the genome. Clear evidence now exists that mutations, rather then being the engine that drives evolution upward, instead are causing degeneration of the genome in harmony with the biblical concept of the Fall and Curse. Evolution, defined strictly as genetic change, does occur, and these changes are a critical component of the creation model that helps to account for the enormous biological diversity seen in the natural world today. However, the types of mutational changes discussed in this review are inconsistent with the evolutionary idea of common decent from ancestral protocells.

Science research has proven the following challenge wrong:

> The church teaches that man was created perfect, and that for six thousand years he was degenerated. Darwin demonstrated the falsity of this dogma. He shows that man has for thousands of ages steadily advanced; that the Garden of Eden is an ignorant myth … and that man did not "fall" (Ingersoll, 1990, pp. 358–359).

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