Chapter 7
Evolution

Contents

7.1 In the Beginning . . .

In the beginning, there was the Big Bang. Then the universe inflated, after which there was only hot plasma of quarks and gluons and other relativistic particles. Particle and antiparticle pairs were continuously formed and destroyed in extreme heat. A small excess of quarks and leptons over antiquarks and antileptons resulted in the predominance of matter over antimatter. At about 10^{-6} s, quarks and gluons combined to form baryons such as protons and neutrons. As the temperature dropped with continuing expansion of universe, no new proton–antiproton or neutron–antineutron pairs could be formed, and a mass annihilation of particle and antiparticle occurred (Kolb and Turner, 1990). In 3 min, the universe was filled with light (photons), and with continued cooling of the universe in the span of 380,000 years, protons became hydrogen by acquiring an electron, photons were decoupled from matter to fly away eventually becoming the microwave background of today. Aggregates of molecules of hydrogen and helium became densely packed with gravity, finally igniting nuclear fusion, forming stars. In about a billion years after the Big Bang, quasars and galaxies began to form. Large populations of stars were born, aged, and died, in spectacular explosions as supernovae, or shrinking into a black hole. Heavier elements including carbon and metals were created in the nuclear

furnace of stars and then scattered in space when the stars went supernova. From the debris of exploded stars, the cosmic dust, new stars were born and new galaxies were formed, continuing the process of cosmic evolution (Bertschinger, 1998).

According to Smolin, black holes may produce other universes, just as our universe seems to have started from a black hole through the Big Bang (Smolin, 1999). In this multiverse theory, there would be many universes, some of which may be adapted to multiply and eventually to produce life, and others would simply shrink back into a black hole and give rise to another universe.

In our universe, by around 9 billion years, or 4,500 million years ago (MA), a small, insignificant planet was formed of cosmic dust in the gravitational system of a medium-sized star called the sun in an outer spiral of the milky way galaxy, an ordinary galaxy among billions (Wikipedia, 2008; Wright, 2004). Early earth was very hot and the atmosphere was composed of hydrogen and helium, much of which flew away escaping earth's gravity. Volcanic activity spewed out gasses that formed the bulk of atmosphere, including H_2O, CO_2, SO_2, CO, S_2, Cl_2, N_2, H_2, NH_3 (ammonia), and CH_4 (methane). As the earth cooled in the Archean period some 3,800 million years ago (MA) to 2,500 MA, H_2O congealed into water; oceans, continental plates, and rocks were formed. Some of the H_2O on the surface of the planet was broken up by ultraviolet rays to form oxygen in the atmosphere.

The atmosphere of the primitive earth was a strongly reducing one, in which glycine was synthesized from formaldehyde and hydrogen cyanide. Adenine was synthesized through hydrogen cyanide polymerization. Various nucleotides may have been formed catalyzed by metals and clay in various parts of the earth including volcanic vents, and some might have also been formed outside earth but arrived in meteorites and comets. So there were places on earth teeming with molecules ready for the next phase of earth's evolution – life (Fig. 7.1).

Perhaps, on a dark and stormy night about 3.5 billion years ago, in the pools of hot soup consisting of water, ammonia, and other organic molecules that were all colliding with each other, copies of some molecules were formed in the mix. Such molecules may have been lowly clay or simple linear polymers (Cairns-Smith, 1982). Some such molecules, particularly those consisting of RNA, found themselves inside spontaneously formed vesicles whose walls consisted of phospholipids (Hanczyc and Szostak, 2004). Such vesicles may spontaneously bud and divide, and those replicating molecules that were kept together in such vesicles and divided had a survival advantage, eventually resulting in stable cells (Fig. 7.2). The RNA in some such vesicles may have attracted the right chemicals to build a cell wall. Some RNA probably formed DNA, a reverse process of modern RNA being copied from DNA. Even a single DNA-containing replicating cell so formed could be the origin of all cells as it gave rise to more cells, most of them identical, but some not, due to copying errors. Copying errors gave rise to *variation* in the offspring cells that in turn had variation.

Some such cells happened to incorporate chemicals within the cell that were able to capture the photons to store energy – photosynthesis by cyanobacteria, which contributed to a change in the composition of the earth's environment by adding more oxygen to it.
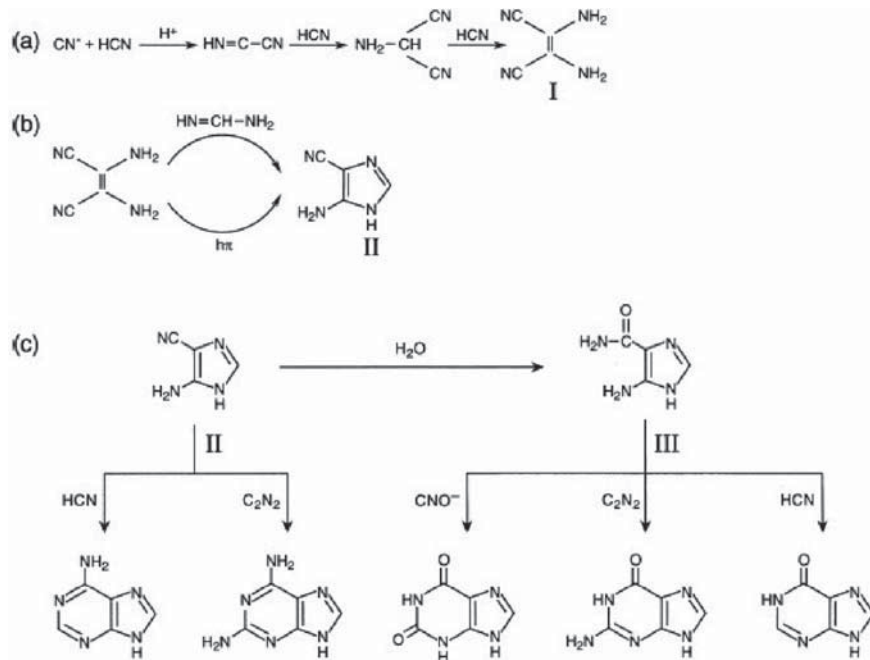
Fig. 7.1 Steps in possible prebiotic syntheses of adenine from HCN. (**a**) The formation of the HCN tetrane. (**b**) The conversion of HCN tetramer to AICN. (**c**) The formation of purines from AICN or from its hydrolysis product 4-amino-imidazole-5-carboxamide (III). From (Orgel, 2004)
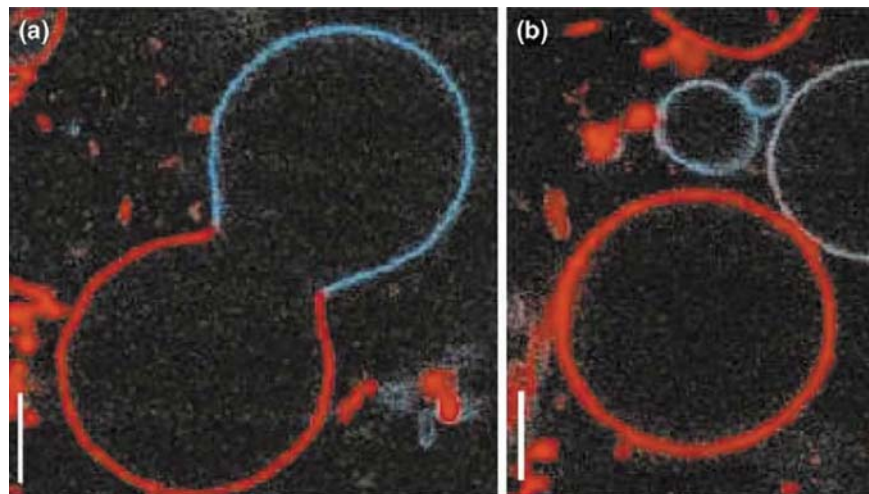

Fig. 7.2 Giant phospholipid vesicles were labeled with two different domain-specific dyes. A fission sequence triggered by heating the vesicles was captured by two-photon microscopy. (From Baumgart et al., 2003, reproduced with permission from Nature)

7.2 In a Changing, Hostile World

As we have seen, the atmosphere of early earth was frankly toxic, but perhaps such a hot atmosphere bombarded by meteorites and infused with gasses and debris from constant volcanic activity might have produced just the kind of mixing and shaking and turmoil to produce the beginnings of life. But life must have been hard for the self-replicating cells, and above all unpredictable. Many replicating molecules and protocells must have been formed, had a brief existence, and then perished in the changing, toxic environment. This constant churning of emergence and destruction of replicating entities resulted in the survival of those that could adapt to the constantly changing environment. Thus arose an algorithm that is evolution (Dennett, 1995), i.e., replicate with errors (variation), and those that can adapt (survive and replicate) in a changed environment will prevail. Evolution is based on *survival of the most stable*, in which survival of the fittest is a special case (Dawkins, 1976) (See Tables 7.1 and 7.2).

As Dennet states, algorithms are *blind* – there is no meaning or direction, just a procedure – in this case, the procedure by which variants that can best replicate in changed environment will survive and replicate again. At this point, it is important to recognize that what is survived is not the cell itself, but the replicators, the information that makes the cell the way it is, i.e., the gene. When we speak of variation, we are really referring to variations in the genetic information. DNA arose from RNA; cells from protocells. Multicellular organisms arose through this algorithm as replication with variation. Replication is more efficient when cells cooperate and effectuate a division of labor – obtaining and storing energy on one hand and replication on the other. Ancient bacteria invaded some cell lines, became incorporated into the cells, and became mitochondria with their own DNA. When such cells divided, they carried the genes (information) for both the original cell (in the nucleus) and the mitochondria (in the cytoplasm where mitochondria reside). Cells and bodies are survival machines for the genes, Dawkins calls evolution a means of perpetuating the *selfish gene* (Dawkins, 1976). This blind procedure, evolution, may lead to many different directions, some fertile, others blind alleys. This procedure, over eons of time, can produce exquisite intricacies in structure as well as complexities that are, in retrospect, functional but stupid, such as the human eye. But we are getting ahead of our story.

7.3 The Selfish Gene

Richard Dawkins clarified the fundamental principle of inheritance of living things in his 1976 landmark book, *The Selfish Gene.* Life as we know it began with naked RNAs that obtained clothes (cell walls), then DNAs arose with instructions for building cells that multiplied. Dawkins saw that all living things are vehicles for strands of DNA with instructions to preserve themselves through the copying process called reproduction. We are all vehicles of genes, and the genes' only interest is their own survival and replication.

It should be clearly stated here that the teleologic figure of speech commonly adopted in discussions of evolution is just that – figure of speech for convenience. Genes do not have any "desire" to replicate or "intention" to survive. It is just that in the course of time, natural laws have it that replicating genes and organisms (or packets of tissue containing genes) that happen to be sturdy (better containers) tend to survive and multiply with the result that "genes that build better vehicles survive and multiply."

For genes to be successful, they require three characteristics: longevity, fecundity, and copying fidelity. In other words, the organism (vehicle) must live long enough to reproduce, and reproduce in large quantities, and the copies must resemble the original.

A severe constraint is placed on the replicating genes by the environment. The environment surrounding the genes (and the vehicles for them, the organisms) consists of other genes and their vehicles, nutrients, toxins, and other hazards. When the resources (e.g., food) are scarce, which was the state of affairs much of the time, then there is naturally competition among the organisms to obtain the resources for survival. From the selfish gene's point of view, then, all other genes that are not like themselves are rivals.

Another resource that is an object of severe competition is a mate for reproduction, as without it, the genes would perish. Organisms better built to find a mate will make more of their own.

From the selfish gene's point of view, altruism is not a problem at all. When particular genes are widely distributed in a group of organisms (vehicles), the act of one vehicle signaling others of danger, even if it risks sacrifice of that particular individual, results in the preservation of large numbers of others that contain the same selfish genes (Fig. 7.3).
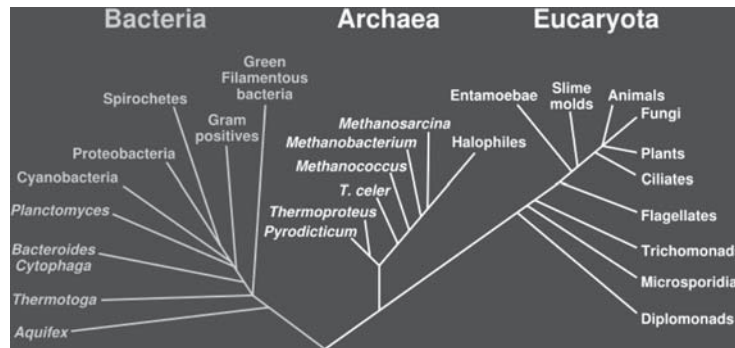
Fig. 7.3 A phylogenetic tree of living things, based on RNA data and proposed by Carl Woese, showing the separation of bacteria, archaea, and eukaryotes. Trees constructed with other genes are generally similar, although they may place some early-branching groups very differently, thanks to long-branch attraction. The exact relationships of the three domains are still being debated, as is the position of the root of the tree. It has also been suggested that due to lateral gene transfer, a tree may not be the best representation of the genetic relationships of all organisms. For instance some genetic evidence suggests that eukaryotes evolved from the union of some bacteria and archaea (one becoming the nucleus and the other the main cell). [Image from Wikimedia, public domain]

7.4 Wonderful Random Errors

Fidelity of copying, a requisite of successful genes, results in the same gene with the same instructions for building the organism. If this fidelity were perfect, then there would be only single-celled organisms inhabiting the earth!

Fortunately for us, nature provided errors for gene replication. Errors in copying resulted in variation and diversity. These errors arose from several factors: pure random statistical errors that occur in any copying process, due to bombardment by waves and particles such as photons, electromagnetic, thermal, and cosmic rays, and other molecules and atoms. Many organisms thus formed by inexact copying were incompatible with life or replication, but some survived, perhaps by dumb luck. And then, the environment changed!

As we know, the earth's crust and atmosphere changed rather drastically over the eons of earth's existence (see Table 7.1). Cells that emerged and replicated in the Archean eon could hardly survive in the oxygen-rich atmosphere of the Proterozoic eon. But the few cells with the errors in DNA so that they could survive in the toxic oxygen atmosphere did survive, and some formed aggregates (e.g., green algae) that resulted in better protection and efficiency in metabolism. Thanks to the random errors, there was variation in the offspring, and the process of evolution of life had begun.

Evolution is, then, the survival of the genes through mutation that are adapting to the demands of changing environment. See Tables 7.1 and 7.2 for an overview of evolution through time on planet earth.

7.5 Wonderful Invention of Sex

A wonderful but puzzling invention relatively early in the course of evolution is sex. From a purely multiplication point of view, sexual reproduction is inefficient, i.e., takes up more energy, slow, and yields less numbers of offsprings compared to asexual reproduction. For example, half of the population (males) does not reproduce directly. Then, why is sex?

The most primitive organisms known to undergo meiosis and to reproduce sexually are protists, the primitive unicellular eukaryotes that arose early in Proterozoic eon (1800 MA). Protists still exist, including those that cause malaria. Perhaps sex originated when some parasites exchanged their genes with the host for transmission and propagation with the host's offspring (Hickey, 1982).

In prokaryotes such as bacteria and archaea that lack a nucleus, genes are typically stored in a single large, circular chromosome, sometimes supplemented by additional small circles of DNA called plasmids, which usually consist of only a few genes. Plasmids are easily transferable between individuals. For example, the plasmids may contain genes that encode for antibiotic resistance. They can be passed between individual cells, even those of different species, via horizontal or lateral gene transfer. Some organisms may have ingested another whose genes may have been incorporated into the host genome.

What is the advantage of such lateral gene transfer? Such newly incorporated genes may have provided survival advantage, i.e., sturdiness, resistance to other parasites. Sex seems to have been optional for most protists with asexual reproduction as needed.

Sex may have arisen as a form of vaccination. Eukaryan fusion sex may have arisen from prokaryan unilateral sex-as-infection (Sterrer, 2002). In prokaryotes, the single circular chromosome is haploid. Their "sex" is unilateral, a donor such as plasmids and bacteriophages penetrates the organism and becomes a genetic symbiont (Snyder and Champness, 1997). It has been reported that in some gram positive bacteria, those lacking a certain plasmid secrete pheromone-like chemicals that attract donors that contain the plasmid and induce conjugation (Dunny et al., 1995). The relationship between the bacteria and their genetic symbionts ranges from antagonistic to mutualistic. Such a symbiont may kill its bacterial host and infect new bacteria laterally, or become integrated into the host's chromosome and be passed on vertically by the replicating host while providing immunity to superinfection by another symbiont of the same type (Sterrer, 2002).

In fact, the emergence of eukaryotes may be due to an infection of bacteria by archae, the prokaryote single cell organism whose genome resembles that of the cellular nucleus. Archae survives even in the present in extreme environments (such as in geysers above 100°C) like those of ancient times (Lopez-Garcia and Moreira, 2006). Alternate theories concerning the origin of cell nucleus include viral infection theory, and exomembrane theory postulates that the nucleus developed when the intracellular elements developed a second membrane enclosing it (de Roos, 2006).

When a symbiont genome became integrated with the host genome in the nucleus, "safe sex" emerged as "reciprocal vaccination." If a mating resulted in additive resistance, then there would have been selective advantage to such diploid heterozygotes (Sterrer, 2002).

With the emergence of multicellular eukaryotic organisms, sex served as reciprocal vaccination of two conspecific genomes. Meiosis and recombination developed as a mechanism of keeping the symbionts in check by breaking them up into fragments and preventing their assembly into large pieces that may return to their original virulence. In order to benefit from the vaccination, the offsprings had to go through the "bottleneck" of having single-celled parents (Maynard Smith and Szathmary, 1995).

The "safe sex" between two complete genomes in eukaryotes marks the distinction between self, mate, and foreign; self being an identical genome. "Mates" are nonidentical but compatible genomes that carry complementary resistance genes, considered to be the origin of mate selection for heterozygosity (Reusch et al., 2001).

Once sex has been invented, there are other reasons why sex is maintained in spite of its costs. One is that sex provides the means for efficient removal of deleterious genes through meiosis and recombination. Diploid organisms can repair a mutated section of the DNA through homologous recombination as there are two copies of

the gene in the cell and one copy is presumably not damaged. Sex also mixes up genes and facilitates the creation and propagation of genes for advantageous traits. The "Red Queen" hypothesis (Bell, 1988) proposes that sex creates unique genotypes that may be better adapted to changing environment, i.e., like the red queen in *Through the Looking Glass* by Lewis Carroll, you have to keep on running (adapting) to remain in the same place (maintain the organism's niche vis-a-vis coevolving organisms such as parasites in the changing environment).

Infection of organisms by others resulting in the infusion and incorporation of new information in the form of genetic instructions seems to have given rise to the wonderful complexity of sex, whose function is to constantly mix up and create new information. This process led to the evolution of most extant living things including ourselves.

7.6 Darwin and Natural Selection

Charles Darwin (1809–1882) proposed the theory of evolution based on careful observation of geologic and biologic evidence in his book, *The Origin of Species* (1859).[1] Darwin was an English naturalist who first studied medicine at Edinburgh University, then theology at Cambridge.

The captain of the expedition ship, HMS Beagle, committed suicide during her first voyage and Captain Robert FitzRoy took over. For the second voyage, FitzRoy decided he needed a "gentleman companion" and hired young Darwin in that capacity. The second voyage of HMS Beagle lasted 5 years though originally planned for two and carried out detailed surveys sailing across the Atlantic Ocean and around the coasts of southern South America, Tahiti, and Australia, circumnavigating the earth. Darwin collected and studied fossils, plants, and animals during the voyage that formed the basis of his theory of evolution and natural selection. Darwin published his journal written during the voyage, *The Voyage of the Beagle*, which earned him a name as a naturalist.

In *The Origin of Species*, he proposed on the basis of his careful observations and other scientific evidences that all species of life evolved over time from common ancestors through the process of natural selection. Alfred Russel Wallace, a naturalist working in Borneo, had similar ideas and communicated them with Darwin, which resulted in a joint publication of Wallace's paper and an abstract of Darwin's forthcoming book. It was Darwin's book, however, that eventually revolutionized science and formed the foundation of biology by providing a unifying principle. Darwin explored human evolution and sexual selection in *The Descent of Man, and Selection In Relation to Sex* (Darwin, 2002–2008; van Wyhe, 2008).

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[1] The original 1859 full book title was *On the Origin of Species by Means of Natural Selection* or the *Preservation of Favoured Races in the Struggle for Life*, which was changed to *The Origin of Species* in the 1872 edition.

Natural selection is the mechanism Darwin proposed in 1859 through which there was a gradual change in the phenotype of some members of the species that was better adapted to a changing environment. Eventually, the gradual change was enough that interbreeding between the changed and unchanged phenotype did not occur, and thus a new species would emerge. Darwin described natural selection as an analogy to artificial selection, in which humans systematically and selectively breed animals with traits desirable to humans until such traits became defining traits of the brood. At the time of Darwin's writing, there was no general theory of inheritance and genetics. It was not until the twentieth century that the works of Gregor Mendel, who was a contemporary of Darwin but whose works lay in obscurity, would be rediscovered (1900 by Hugo de Vries and Carl Correns), and molecular genetics would emerge with the discovery of DNA as genes (1943 by Oswald Avery) and the structure of DNA as double helix (1953 by James Watson and Francis Crick). The discovery and elucidation of the DNA-based molecular mechanisms of genetic inheritance gave rise to modern evolutionary theory. See Figures 7.5 and 7.6.

Darwin's illustrations of beak variation in the finches of the Galápagos Islands hold 13 closely related species that differ most markedly in the shape of their beaks. The beak of each species is suited to its preferred food, suggesting that beak shapes evolved by natural selection (Fig. 7.4).

Fitness is a central concept of natural selection. Though Darwin's term, *survival of the fittest*, implies individual survival, natural selection is in fact based on reproductive success. The phenotypes that lead to most number of offsprings will prevail. In addition to natural selection, Darwin described *sexual selection* as a means of gradual accentuation of traits that do not have survival advantage, for example, peacock's tail. Sexual selection is based on advantages in competing for a mate for reproduction.

Fig. 7.4 Darwin's Finches. Journal of researches into the natural history and geology of the countries visited during the voyage of HMS Beagle round the world, under the command of Captain Fitz Roy, R.N. 2nd edition. From Darwin's 1845 book, "Voyage of the Beagle" this image is in the public domain because its copyright has expired in those countries with a copyright term of life of the author plus 100 years or less [from Wikimedia]

1. Geospiza magnirostris
2. Geospiza fortis
3. Geospiza parvula
4. Certhidea olivacea

Finches from Galapagos Archipelago

Fig. 7.5 An overview of the structure of DNA
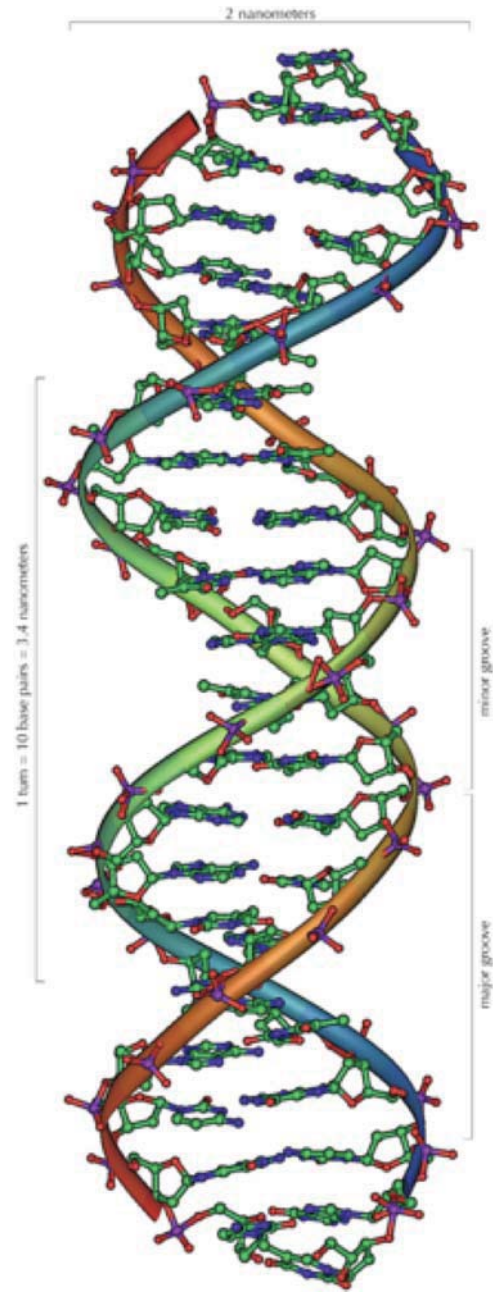
Fig. 7.6 Chemical structure of DNA. The backbone of the DNA strand is made from alternating phosphate and sugar residues. The sugars are joined together by phosphate groups that form phosphodiester bonds between the third and fifth carbon atoms of adjacent sugar rings. These asymmetric bonds mean a strand of DNA has a dire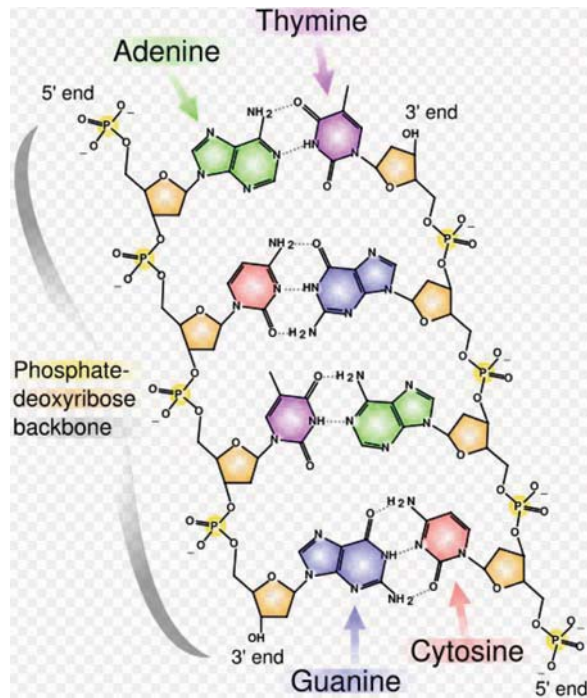ction. In a double helix the direction of the nucleotides in one strand is opposite to their direction in the other strand. The asymmetric ends of DNA strands are referred to as the 5′ (*five prime*) and 3′ (*three prime*) ends. One of the major differences between DNA and RNA is the sugar, with 2-deoxyribose being replaced by the alternative pentose sugar ribose in RNA. The DNA double helix is stabilized by hydrogen bonds between the bases attached to the two strands. The four bases found in DNA are adenine (A), cytosine (C), guanine (G), and thymine (T). These bases are classified into two types; adenine and guanine are fused five- and six-membered heterocyclic compounds called purines, while cytosine and thymine are six-membered rings called pyrimidines. A fifth pyrimidine base, called uracil (U), usually takes the place of thymine in RNA and differs from thymine by lacking a methyl group on its ring. Uracil is not usually found in DNA, occurring only as a breakdown product of cytosine [From Wikipedia]. *Permission is granted to copy, distribute and/or modify this document under the terms of the* "GNU Free Documentation License," Version 1.2 or any later version published by the Free Software Foundation; with no Invariant Sections, no Front-Cover Texts, and no Back-Cover Texts. A copy of the license is included in the section entitled "GNU Free Documentation License" [From Wikimedia]

George C. Williams first explicitly advocated the gene-centric view of evolution in his 1966 book *Adaptation and Natural Selection*. He proposed an evolutionary concept of gene in which natural selection favored some genes over others.

Richard Dawkins argued in *The Selfish Gene* (Dawkins, 1976) and *The Extended Phenotype* (Dawkins, 1982) that the gene is the only replicator in living systems.

He argued that only genes transmit their structure largely intact and are potentially immortal through the copying process. Therefore, genes are the units of selection. Dawkins redefines the word "gene" to mean "an inheritable unit" instead of the generally accepted definition of "a section of DNA coding for a particular protein." Dawkins describes the idea of gene-centric selection in *River Out of Eden* by describing life as a river of compatible genes flowing through geological time. Scoop up a pail of genes from the river of genes, and we have an organism serving as temporary survival machines for the genes. A river of genes may fork into two or more branches representing noninterbreeding species as a result of geographical separation.

In gene-centric view of evolution, a gene need not have a function in the construction of the phenotype as long as the organism will keep on reproducing the vessels for the gene. The so-called junk DNA may be an example. "Junk" DNA does not contain instructions for protein coding, but they may be critically important to an organism's evolutionary survival by affecting others that do or by affecting the stability of the chromosome itself. In one study with the fruit fly (*Drosophila melanogaster*), the "junk DNA" regions, which account for about 80% of the fly's total genome, were found to be evolving more slowly than expected due to natural selection pressures on the nonprotein-coding DNA to remain the same over time. The "junk" regions also exhibit an unusually large amount of functional genetic divergence between different species of *Drosophila*. This implies that, like evolutionary changes to proteins, changes to these "junk" parts of the genome also play an important role in the evolution of new species. The largest differences between major species groups including fruit flies, reptiles, and mammals seem to be the amount of "junk" DNA rather than the number of genes (Andolfatto, 2005).

7.7 Somatic Evolution

We have seen that our bodies may be conceptualized as temporary containers for genes that attain immortality through replication. To be precise, however, it is the cells in our bodies that contain the genes. It is natural, then, to expect evolutionary processes occurring at the cellular level. Indeed, such somatic evolution plays an important role in both disease and health.

Somatic evolution of neurons is an extremely important topic for our purposes and will be discussed in Chapter 8.

Somatic evolution has been extensively studied in cancer. Some cells undergo mutation that increases cell growth and others may have already mutated oncogenes in them. For example, the human colonic epithelium is renewed every 3–5 days. For such a high rate of turnover, there are large numbers of cells undergoing mitoses and, therefore, large number of mutations. Cancers develop through genomic instability, which generates diversity, from which clonal evolution may occur. In colorectal cancers, three identifiable processes involved in generating diversity at the genetic or epigenetic level have been reported (Boland and Goel, 2005). Colorectal cancers may have chromosomal instability (CIN), microsatellite instability (MSI), or the

CpG island methylator phenotype (CIMP). Each of these processes is reported to be associated with a unique mutational or epigenetic "signature" identifiable in the tumor cells.

After acquiring somatic mutations for cell growth, some of the cancer cells may evolve to escape from the control of the microenvironment that is designed to keep them in place through various messenger systems. Not all mutated cells can do this, some may undergo enhanced proliferation without escaping environmental control. For example, the prevalence of small thyroid tumors in postmortem examination of people between the ages of 50–70 was 36%, while the incidence of clinically apparent thyroid cancer in age-matched population was 0.1% (Harach et al., 1985).

Most cancer cells are aneuploid (abnormal number of chromosomes), which is often manifested by the gain or loss of a whole of parts of chromosomes. Tumor cells often have excess chromosomes, often 60–90 per cell. There may be other chromosomal abnormalities such as deletions, inversions, duplications, and translocations. Such chromosomal abnormalities often result in loss of heterozygosity of particular genes. In an average tumor, about 25–30% of the normal alleles are lost, in some cases as high as 75% (Lengauer et al., 1998). The loss of these alleles, especially those of tumor suppressor and cell–cell adhesion control genes, may benefit the rapidly replicating clonal populations of tumor cells as they allow cells to rapidly adapt to the changing microenvironment (Smalley et al., 2005).

The effects of environmental evolutionary pressure on tumor cells have been demonstrated in experimental models. The sequential passage of melanoma cells through a reconstituted basement membrane (which mimics invasion into the dermal microenvironment) or in serum-free media selects for clones that are tenfold more invasive, metastatic and grow more rapidly in both serum-free and growth factor-depleted media (Kath et al., 1991). The selected invasive melanoma cells required continuous evolutionary pressure to maintain their phenotype and reverted to the parental phenotype when the environmental stimuli were removed. Although the effects of environmental selection pressure pushed the parent cells toward a more aggressive phenotype, it seems that these changes were not fixed.

It appears that the tumor cell clones that manage to escape their local environment have lost strong cell to cell contact with their neighbors and are no longer dependent on exogenous environmental cues to regulate their behavior (Smalley et al., 2005). In most cancers, a critical first step in this local escape seems to be a downregulation of E-cadherin expression or function. In melanoma, the first step in the transformation is the escape from keratinocyte control. As keratinocytes regulate melanocyte growth very tightly, loss of keratinocyte–melanocyte interaction at an early stage permits the earliest rounds of clonal expansion. E-cadherin inactivation or loss is required for escape of the earliest tumor cells from the primary focus (Hirohashi, 1998). Melanoma cells also undergo a cadherin switch and upregulate expression of N-cadherin (Hsu et al., 1996). There is evidence that the upregulation of N-cadherin rather than loss of E-cadherin is more important for the invasive and metastatic behavior of cancer cells. Upregulation of N-cadherin results in a number of survival advantages, such as reducing the rate of apoptosis, and less strong cell–cell adhesion thereby permitting greater mobility.

Immunocytes that are important in resistance to invading organisms through the production of antibodies have been demonstrated to evolve through clonal selection. The enormous diversity in antibody-producing cells is achieved by a variety of mechanisms including somatic recombination and mutation (Edelman, 1994).

7.8 Universal Darwinism

The process of evolution by natural selection is not unique to living things, though Darwin first proposed it as an explanation of how species evolved from common ancestors over time. To the extent that environment changes and entities (organic or nonorganic) arise and disintegrate, natural selection takes place so that entities that are better adapted to the changing environment will tend to become more numerous. This principle has been applied to quantum physics to explain the emergence of classical reality from quantum reality (Ollivier et al., 2004; Zurek, 2007). In quantum wave function, decoherence resulting from interference from outside (e.g., observation) gives rise to existence of individual particles, the location of which is statistical, i.e., many possible realities. Among all such possible realities, only those that can interact with the environment and decohere (i.e., become real) can produce information progeny.

Darwinian natural selection has been proposed as the mechanism by which the current universe evolved from many possible universes that evolved from a series of bouncing black holes that gave rise to daughter universes (Smolin, 1999, 2004, 2006). Smolin states that the physical processes that strongly influence the number of black holes produced are nucleosynthesis, galaxy formation, star formation, stellar dynamics, supernova explosions, and the formation and stability of neutron stars. Through the process of such cosmic evolution, our universe may have developed complexity enough to produce civilizations like ours.

Appendix

Table 7.1 Geologic timescale (From Wikipedia, the free encyclopedia)

Graphical timelines

The second and third timelines are each subsections of their preceding timeline as indicated by asterisks.

Millions of Years
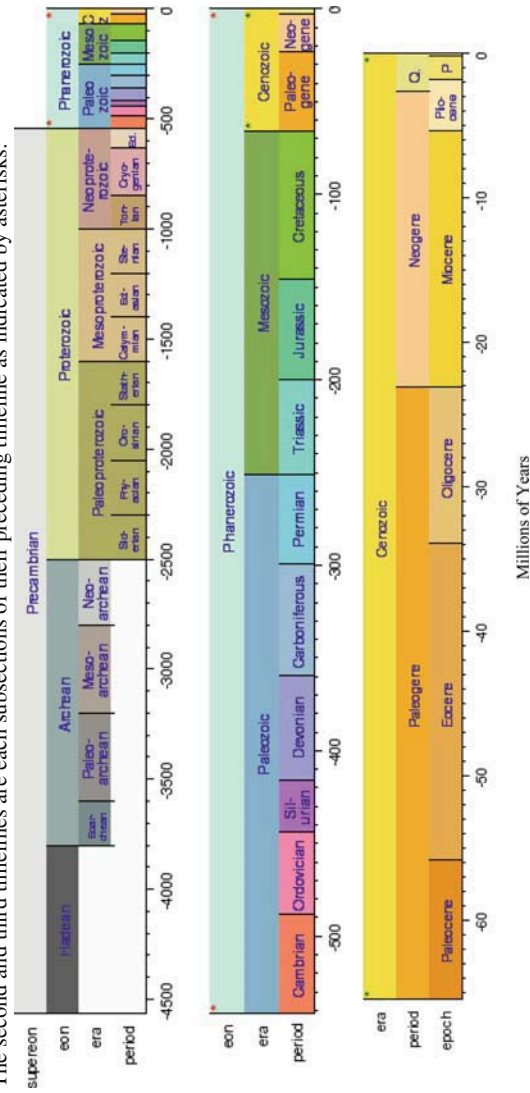
The Holocene (*the latest epoch*) *is too small to be shown clearly on this timeline.*

Table 7.2 Table of geologic time (From Wikipedia. All text I saw available under the terms of the GNU-Free Documentation License). The table summarizes the major events and characteristics of the periods of time making up the geologic timescale. As above, this timescale is based on the International Commission on Stratigraphy. (See *lunar geologic timescale* for a discussion of the geologic subdivisions of Earth's moon.) The height of each table entry does not correspond to the duration of each subdivision of time. As this table is a subsection of the Wickipedia article, the citations do not begin with 1 and a.

v · d · e Geologic timescale template

Supereon	Eon	Era	Period[6]	Series/ epoch	Faunal stage/geologic age	Major events	Start, million years ago[7]
	Phanerozoic	Cenozoic	Neogene[8]	Holocene	Quaternary	The last glacial period ends and rise of human civilization	0.011430 ± 0.00013[9]
				Pleistocene	Late/Tyrrhenian Stage	Flourishing and then extinction of many large mammals (*Pleistocene megafauna*)	0.126 ± 0.005*
						Evolution of anatomically modern humans	
					Middle		0.500?
					Early		1.806 ± 0.005*
					Gelasian		2.588 ± 0.005*
				Pliocene	Piacenzian/ Blancan	Intensification of present ice age; cool and dry climate.	3.600 ± 0.005*
						Australopithecines, many of the existing genera of mammals, and recent mollusks appear. *Homo habilis* appears. Present ice age begins	
					Zanclean		5.332 ± 0.005*

Table 7.2 (continued)

v · d · e Geologic timescale template

Supereon	Eon	Era	Period[6]	Series/epoch	Faunal stage/geologic age	Major events	Start, million years ago[7]
				Miocene	Messinian	Moderate climate; Orogeny in northern hemisphere. Modern mammal and bird families became recognizable. Horses and mastodons diverse Grasses become ubiquitous. First apes appear (for reference see the article: "Sahelanthropus tchadensis")	$7.246 \pm 0.05^*$
					Tortonian		$11.608 \pm 0.05^*$
					Burdigalian		$13.65 \pm 0.05^*$
					Serravallian		$15.97 \pm 0.05^*$
					Langhian		$20.43 \pm 0.05^*$
					Aquitanian		$23.03 \pm 0.05^*$
			Paleogene[8]	Oligocene	Chattian	Warm climate; rapid evolution and diversification of fauna, especially mammals. Major evolution and dispersal of modern types of flowering plants	$28.4 \pm 0.1^*$
					Rupelian		$33.9 \pm 0.1^*$

$v \cdot d \cdot e$ Geologic timescale template

Table 7.2 (continued)

Supereon	Eon	Era	Period[6]	Series/epoch	Faunal stage/geologic age	Major events	Start, million years ago[7]
				Eocene	Priabonian	Archaic mammals (e.g., Creodonts, Condylarths, Uintatheres) flourish and continue to develop during the epoch. Appearance of several "modern" mammal families. Primitive whales diversify. First grasses. Reglaciation of Antarctica and formation of its ice cap; current ice age begins	$37.2 \pm 0.1^*$
					Bartonian		$40.4 \pm 0.2^*$
					Lutetian		$48.6 \pm 0.2^*$
					Ypresian		$55.8 \pm 0.2^*$
				Paleocene	Thanetian	Climate tropical. Modern plants appear; Mammals diversify into a number of primitive lineages following the extinction of the dinosaurs. First large mammals (up to bear or small hippo size)	$58.7 \pm 0.2^*$
					Selandian		$61.7 \pm 0.3^*$
					Danian		$65.5 \pm 0.3^*$

Table 7.2 (continued)

v · d · e Geologic timescale template

Supereon	Eon	Era	Period[6]	Series/epoch	Faunal stage/geologic age	Major events	Start, million years ago[7]
		Mesozoic	Cretaceous	Upper/late	Maastrichtian	Flowering plants proliferate, along with new types of insects. More modern teleost fish begin to appear Ammonites, belemnites, rudist bivalves, echinoids and sponges all common. Many new types of dinosaurs (e.g., Tyrannosaurs, Titanosaurs, duck bills, and horned dinosaurs) evolve on land, as do Eusuchia (modern crocodilians); and mosasaurs and modern sharks appear in the sea Primitive birds gradually replace pterosaurs Monotremes, marsupials, and placental mammals appear. Break up of Gondwana	70.6 ± 0.6*
					Campanian		83.5 ± 0.7*
					Santonian		85.8 ± 0.7*
					Coniacian		89.3 ± 1.0*
					Turonian		93.5 ± 0.8*
					Cenomanian		99.6 ± 0.9*
				Lower/early	Albian		112.0 ± 1.0*
					Aptian		125.0 ± 1.0*
					Barremian		130.0 ± 1.5*
					Hauterivian		136.4 ± 2.0*

Table 7.2 (continued)

$v \cdot d \cdot e$ Geologic timescale template

Supereon	Eon	Era	Period[6]	Series/epoch	Faunal stage/geologic age	Major events	Start, million years ago[7]
			Jurassic	Upper/late	Valanginian	Gymnosperms (especially conifers, Bennettitales, and cycads) and ferns common. Many types of dinosaurs, such as sauropods, carnosaurs, and stegosaurs. Mammals common but small. First birds and lizards. Ichthyosaurs and plesiosaurs diverse. Bivalves, Ammonites, and belemnites abundant. Sea urchins very common, along with crinoids, starfish, sponges, and terebratulid and rhynchonellid brachiopods. Breakup of Pangaea into Gondwana and Laurasia	$140.2 \pm 3.0^*$
					Berriasian		$145.5 \pm 4.0^*$
					Tithonian		$150.8 \pm 4.0^*$
					Kimmeridgian		$155.7 \pm 4.0^*$
					Oxfordian		$161.2 \pm 4.0^*$
				Middle	Callovian		164.7 ± 4.0
					Bathonian		$167.7 \pm 3.5^*$
					Bajocian		$171.6 \pm 3.0^*$
					Aalenian		$175.6 \pm 2.0^*$
				Lower/early	Toarcian		$183.0 \pm 1.5^*$

Table 7.2 (continued)

$v \cdot d \cdot e$ Geologic timescale template

Supereon	Eon	Era	Period[6]	Series/ epoch	Faunal stage/geologic age	Major events	Start, million years ago[7]
			Triassic	Upper/late	Pliensbachian		$189.6 \pm 1.5^*$
					Sinemurian		$196.5 \pm 1.0^*$
					Hettangian		$199.6 \pm 0.6^*$
					Rhaetian	Archosaurs dominant on land as dinosaurs, in the oceans as Ichthyosaurs and nothosaurs, and in the air as pterosaurs. Cynodonts become smaller and more mammal like, while first mammals and crocodilia appear. *Dicrodium* flora common on land. Many large aquatic temnospondyl amphibians Ceratitic ammonoids extremely common. Modern corals and teleost fish appear, as do many modern insect clades	$203.6 \pm 1.5^*$
					Norian		$216.5 \pm 2.0^*$
					Carnian		$228.0 \pm 2.0^*$
				Middle	Ladinian		$237.0 \pm 2.0^*$
					Anisian		$245.0 \pm 1.5^*$
				Lower/early ("Scythian")	Olenekian		$249.7 \pm 1.5^*$
					Induan		$251.0 \pm 0.7^*$

$v \cdot d \cdot e$ Geologic timescale template

Table 7.2 (continued)

Supereon	Eon	Era	Period[6]	Series/epoch	Faunal stage/geologic age	Major events	Start, million years ago[7]
		Paleozoic	Permian	Lopingian	Changhsingian	Landmasses unite into supercontinent Pangaea, creating the Appalachians. End of Permo-Carboniferous glaciation. Synapsid reptiles (pelycosaurs and therapsids) become plentiful, while parareptiles and temnospondyl amphibians remain common. In the mid-Permian, coal-age flora are replaced by cone-bearing gymnosperms (the first true seed plants) and by the first true mosses. Beetles and flies evolve. Marine life flourishes in warm shallow reefs; productid and spiriferid brachiopods, bivalves, forams, and ammonoids all abundant. Permian-Triassic extinction event occurs 251 mya: 95% of life on Earth becomes extinct, including all trilobites, graptolites, and blastoids	253.8 ± 0.7*
					Wuchiapingian		260.4 ± 0.7*
				Guadalupian	Capitanian		265.8 ± 0.7*

Table 7.2 (continued)

v · d · e Geologic timescale template

Supereon	Eon	Era	Period[6]	Series/epoch	Faunal stage/geologic age	Major events	Start, million years ago[7]
				Cisuralian	Wordian/Kazanian		268.4 ± 0.7*
					Roadian/Ufimian		270.6 ± 0.7*
					Kungurian		275.6 ± 0.7*
					Artinskian		284.4 ± 0.7*
					Sakmarian		294.6 ± 0.8*
					Asselian		299.0 ± 0.8*
			Carboniferous[10]/ Pennsylvanian	Upper/Late	Gzhelian	Winged insects radiate suddenly; some (esp. Protodonata and Palaeodictyoptera) are quite large. Amphibians common and diverse. First reptiles and coal forests (scale trees, ferns, club trees, giant horsetails, *Cordaites*, etc.). Highest-ever atmospheric oxygen levels. Goniatites, brachiopods, bryozoa, bivalves, and corals plentiful in the seas and oceans. Testate forams proliferate	303.9 ± 0.9*
				Middle	Kasimovian		306.5 ± 1.0*
					Moscovian		311.7 ± 1.1*
				Lower/Early	Bashkirian		318.1 ± 1.3*

Table 7.2 (continued)

$v \cdot d \cdot e$ Geologic timescale template

Supereon	Eon	Era	Period[6]	Series/epoch	Faunal stage/geologic age	Major events	Start, million years ago[7]
			Carbon-iferous[10]/Mississippian	Upper/late	Serpukhovian	Large primitive trees, first land vertebrates, and amphibious sea-scorpions live amid coal-forming coastal swamps Lobe-finned rhizodonts are dominant big fresh-water predators. In the oceans, early sharks are common and quite diverse; echinoderms (especially crinoids and blastoids) abundant. Corals, bryozoa, goniatites, and brachiopods (Productida, Spiriferida, etc.) very common. But trilobites and nautiloids decline. Glaciation in East Gondwana	326.4 ± 1.6*
				Middle	Viséan		345.3 ± 2.1*
				Lower/early	Tournaisian		359.2 ± 2.5*

Table 7.2 (continued)

$v \cdot d \cdot e$ Geologic timescale template

Supereon	Eon	Era	Period[6]	Series/epoch	Faunal stage/geologic age	Major events	Start, million years ago[7]
			Devonian	Upper/late	Famennian	First clubmosses, horsetails, and ferns appear, as do the first seed-bearing plants (progymnosperms), first trees (the progymnosperm *Archaeopteris*), and first (wingless) insects Strophomenid and atrypid brachiopods, rugose and tabulate corals, and crinoids are all abundant in the oceans. Goniatite ammonoids are plentiful, while squid-like coleoids arise. Trilobites and armored agnaths decline, while jawed fishes (placoderms, lobe-finned and ray-finned fish, and early sharks) rule the seas. First amphibians still aquatic. "Old Red Continent" of Euramerica	374.5 ± 2.6*
				Middle	Frasnian		385.3 ± 2.6*
					Givetian		391.8 ± 2.7*
					Eifelian		397.5 ± 2.7*
				Lower/early	Emsian		407.0 ± 2.8*
					Pragian		407.0 ± 2.8*
					Lochkovian		416.0 ± 2.8*

Table 7.2 (continued)

v · d · e Geologic timescale template

Supereon	Eon	Era	Period[6]	Series/ epoch	Faunal stage/geologic age	Major events	Start, million years ago[7]
			Silurian	Pridoli	*No faunal stages defined*	First vascular plants (the rhyniophytes and their relatives), first millipedes, and arthropleurids on land. First jawed fishes, as well as many armored jawless fish, populate the seas. Sea-scorpions reach large size. Tabulate and rugose corals, brachiopods (*Pentamerida*, Rhynchonellida, etc.), and crinoids all abundant. Trilobites and mollusks diverse; graptolites not as varied	$418.7 \pm 2.7^{*}$
				Ludlow/Cayugan	Ludfordian		$421.3 \pm 2.6^{*}$
					Gorstian		$422.9 \pm 2.5^{*}$
				Wenlock	Homerian/ Lockportian		$426.2 \pm 2.4^{*}$
					Sheinwoodian/ Tonawandan		$428.2 \pm 2.3^{*}$
				Llandovery/ Alexandrian	Telychian/ Ontarian		$436.0 \pm 1.9^{*}$
					Aeronian		$439.0 \pm 1.8^{*}$
					Rhuddanian		$443.7 \pm 1.5^{*}$

Table 7.2 (continued)

$v \cdot d \cdot e$ Geologic timescale template

Supereon	Eon	Era	Period[6]	Series/ epoch	Faunal stage/geologic age	Major events	Start, million years ago[7]
			Ordovician	Upper/late	Hirnantian	Invertebrates diversify into many new types (e.g., long straight-shelled cephalopods). Early corals, articulate brachiopods (*Orthida*, *Strophomenida*, etc.), bivalves, nautiloids, trilobites, ostracods, bryozoa, many types of echinoderms (crinoids, cystoids, starfish, etc.), branched graptolites, and other taxa all common. Conodonts (early planktonic vertebrates) appear. First green plants and fungi on land. Ice age at end of period	445.6 ± 1.5*
					Other faunal stages		460.9 ± 1.6*
				Middle	Darriwilian other faunal stages		468.1 ± 1.6* 471.8 ± 1.6*
				Lower/early	Arenig		471.8 ± 1.7*
					Tremadocian		488.3 ± 1.7*

Table 7.2 (continued)

v · d · e Geologic timescale template

Supereon	Eon	Era	Period[6]	Series/epoch	Faunal stage/geologic age	Major events	Start, million years ago[7]
			Cambrian	Furongian	Other faunal stages	Major diversification of life in the Cambrian Explosion. Many fossils; most modern animal phyla appear. First chordates appear, along with a number of extinct, problematic phyla. Reef-building Archaeocyatha abundant; then vanish. Trilobites, priapulid worms, sponges, inarticulate brachiopods (unhinged lampshells), and many other animals numerous. Anomalocarids are giant predators, while many Ediacaran fauna die out. Prokaryotes, protists (e.g., forams), fungi, and algae continue to present day. Gondwana emerges	496.0 ± 2.0*
					Paibian/Ibexian/ Ayusokkanian/ Sakian/Aksayan		501.0 ± 2.0*
				Middle	Other faunal stages		513.0 ± 2.0
				Lower/early	Other faunal stages		542.0 ± 1.0*

Table 7.2 (continued)

v · d · e Geologic timescale template

Supereon	Eon	Era	Period[6]	Series/epoch	Faunal stage/geologic age Major events	Start, million years ago[7]
Precambrian[11]	Proterozoic[12]	Neoproterozoic	Ediacaran		Good fossils of the first multi-celled animals. Ediacaran biota flourish worldwide in seas. Simple trace fossils of possible worm-like *Trichophycus*, etc. First sponges and trilobitomorphs. Enigmatic forms include many soft-jellied creatures shaped like bags, disks, or quilts (like *Dickinsonia*)	630 +5/−30*
			Cryogenian		Possible "Snowball Earth" period. Fossils still rare. Rodinia landmass begins to break up	850[13]
			Tonian		Rodinia supercontinent persists. Trace fossils of simple multi-celled eukaryotes. First radiation of dinoflagellate-like acritarchs	1000[13]
		Mesoproterozoic	Stenian		Narrow highly metamorphic belts due to orogeny as Rodinia formed	1200[13]
			Ectasian		Platform covers continue to expand. Green algae colonies in the seas	1400[13]
			Calymmian		Platform covers expand	1600[13]
		Paleoproterozoic	Statherian		First complex single-celled life: protists with nuclei. Columbia is the primordial supercontinent	1800[13]
			Orosirian		The atmosphere became oxygenic. Vredefort and Sudbury Basin asteroid impacts. Much orogeny	2050[13]
			Rhyacian		Bushveld formation formed. Huronian glaciation	2300[13]
			Siderian		Oxygen catastrophe: banded iron formations formed	2500[13]
	Archean[11]	Neoarchean			Stabilization of most modern cratons; possible mantle overturn event	2800[13]
		Mesoarchean			First stromatolites (probably colonial cyanobacteria). Oldest macrofossils	3200[13]
		Paleoarchean			First known oxygen-producing bacteria. Oldest definitive microfossils	3600[13]
		Eoarchean			Simple single-celled life (probably bacteria and perhaps archaea). Oldest probable microfossils	3800
	Hadean[11, 12, 14]	Lower Imbrian[12]			This era overlaps the end of the late heavy bombardment of the inner solar system	c.3850

Table 7.2 (continued)

v · d · e Geologic timescale template

Supereon	Eon	Era	Period[6]	Series/epoch	Faunal stage/geologic age Major events	Start, million years ago[7]
		Nectarian[12]			This era gets its name from the lunar geologic timescale when the Nectaris Basin and other major lunar basins were formed by large impact events	c.3920
		Basin Groups[12]			Oldest known rock (4,100 Ma). The first lifeforms self-replicating RNA molecules may have evolved on earth around 4 bya during this era	c.4150
		Cryptic[12]			Oldest known mineral (Zircon, 4,400 Ma). Formation of Earth (4,567.17–4,570 Ma)	c.4570

[6]Paleontologists often refer to faunal stages rather than geologic (geological) periods. The stage nomenclature is quite complex. See The Paleobiology Database. Retrieved on March 19, 2006 for an excellent time ordered list of faunal stages.

[7]Dates are slightly uncertain with differences of a few percent between various sources being common. This is largely due to uncertainties in radiometric dating and the problem that deposits suitable for radiometric dating seldom occur exactly at the places in the geologic column where they would be most useful. The dates and errors quoted above are according to the International Commission on Stratigraphy 2004 time scale. Dates labeled with a* indicate boundaries where a Global Boundary Stratotype Section and Point has been internationally agreed upon: see List of Global Boundary Stratotype Sections and Points for a complete list.

[8] a b Historically, the Cenozoic has been divided up into the Quaternary and Tertiary sub-eras, as well as the Neogene and Paleogene periods. However, the International Commission on Stratigraphy has recently decided to stop endorsing the terms Quaternary and Tertiary as part of the formal nomenclature.

[9] The start time for the Holocene epoch is here given as 11,430 years ago ± 130 years (that is, between 9610 BC–9560 BC and 9350 BC–9300 BC). For further discussion of the dating of this epoch, see Holocene.

[10] a b In North America, the Carboniferous is subdivided into Mississippian and Pennsylvanian Periods.

[11] a b c The Precambrian is also known as Cryptozoic.

[12] a b c d e f The Proterozoic, Archean, and Hadean are often collectively referred to as the Precambrian Time or sometimes, also the Cryptozoic.

[13] a b c d e f g h i j k l Defined by absolute age (Global Standard Stratigraphic Age).

[14] Though commonly used, the Hadean is not a formal eon and no lower bound for the Archean and Eoarchean have been agreed upon. The Hadean has also sometimes been called the Priscoan or the Azoic. Sometimes, the Hadean can be found to be subdivided according to the *lunar geologic time scale*. These eras include the Cryptic and Basin Groups (which are subdivisions of the pre-Nectarian era), Nectarian, and lower Imbrian eras.

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