The Enlightenment of Evolutionary Medicine

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The Past and Future of Human Diseases

By

Aaron J. W. Hsueh

Cambridge Scholars Publishing

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Nothing in biology [or medicine] makes sense except in
the light of evolution.
—Theodosius Dobzhansky (1900-1975)

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FOREWORD

It took a visionary in the person of Professor Aaron J.W. Hsueh to bring us back to our senses. *Enlightenment of Evolutionary Medicine: Past and Future of Human Diseases* makes it plain. We have all lost sight of the ever-expanding fruits of evolution and the likely modifications thereof. Little did we realize how much has changed since the 1859 publication of *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*. Nor did we realize that human evolution can no longer be deemed to constitute a passive, slow-paced, stepwise, hands-free affair. The discovery of DNA, the very essence of heredity, changed everything. Recombinant DNA technologies, DNA amplification systems, DNA sequencing prowess, and unprecedented genetic engineering capabilities have ushered in the age of evolutionary medicine. It follows that the plodding pace of natural selection is being eclipsed when and if modern humans are concerned. Stated differently, natural selection is being supplanted by the tools of evolutionary medicine. Evolution "on steroids" is finally upon us.

As Professor Hsueh makes plain, we did not realize that evolutionary medicine is bound to change life as we knew it by "simply" uncovering the diversity of the molecular signatures undergirding it all. Mastering the evolution of the hemoglobin family may all but see to the vanquishment of sickle cell disease. Uncovering new hormones and their receptors holds the promise of heretofore unthinkable diagnostic tools and treatment paradigms. Appreciating the molecular diversity of hormonal signaling by members of the phosphodiesterase enzyme family is bound to give rise to new and important drug candidates. This and much more, are carefully and exhaustively covered by Professor Hsueh, whose very own scientific contributions are part of this unprecedented tapestry of insights. Never before have the extant fruits of evolution been so thoroughly and carefully delineated with human well-being in mind.

Writing as I do in the thick of the COVID-19 pandemic, I cannot help but note that evolutionary medicine may well, or perhaps should, harbor loftier goals for mankind. Watching the wreckage wrought by the COVID-19 pandemic, one cannot help but conclude that natural selection let us down. All indications are that the human species is just as inept at handling the family of SARS-associated coronaviruses as it was a century ago when faced with the 1918 pandemic influenza. None of this would have surprised Charles Robert Darwin. After all, evolutionary progress is to be measured over millennia. No more. Enter evolutionary medicine replete with the tools to accelerate evolution like never before by switching from the passive to the active. Is it not about time that we reengineered the human immune system in a manner that would render the toll of pandemics a thing of the past? Is it not our responsibility to do so? As Professor Hsueh carefully sketches out, evolutionary medicine could take us there.

It is rare that one comes across a book that takes on a panorama as sweeping as *Enlightenment of Evolutionary Medicine: Past and Future of Human Diseases*. Failing to take it all in risks leaving one in the dark at a point in human history when evolution transitions from the passive to the active and from the disinterested to the self-interested. The numbing pace of natural selection is no more. Welcome to a raging future.

Eli Y. Adashi, MD, MS, MA (ad eundem),
CPE, FACOG, FRCOG (ad eundem)
Professor of Medical Science
Former Dean of Medicine and Biological Sciences
Brown University, USA

PREFACE

The biggest breakthrough in biology in the 19th century was Darwin's theory of evolution, and the biggest breakthrough in biology in the 20th century was the sequencing of the human genome. At the beginning of the 21st century, we can combine evolutionary theory with genomics to further understand biology and medicine. This book is an attempt to use the theory of evolution to understand modern medicine. Since 2019, I have been pleased to offer the yearly course "Evolution and Modern Medicine" at Fudan University School of Basic Medicine, China. This book is condensed from the course's thirty hours of lecture content.

Only from the point of view of evolution can we truly understand biology and medicine. This book will first introduce Darwin's original contribution and the fossil evidence of evolution, and then talk about natural selection, sexual selection, and artificial selection. On the role of artificial selection in the evolutionary process, the importance of artificial selection of animals and plants on the development of human civilization will be described, emphasizing active and passive artificial selection, together with the scientific basis for not opposing genetically modified foods. Then, we will look at the origin of species, the co-evolution of species, and the origin of life. After discussing Mendelian genetics, Morgan's chromosome theory, and the sequencing of genomes from diverse species, we will emphasize the genetic basis of evolution, including the concept of gene pools, gene drift, chromosome homology, and the evolution of orthologous and paralogous genes in different organisms. We will further talk about the relationship between epigenetics and evolution. On the topic of evo-devo, we will discuss the development from animal embryos to adults and developmental plasticity, explaining why the fingerprints of identical twins are different. We will discuss how a small group of homologous genes can regulate the diverse phenotypes between fruit flies and humans. After focusing on the evolutionary basis of eye development ranging from flies to human beings, we will also touch on humans having three pairs of unique kidneys during embryonic development.

When discussing Darwinian medicine, we will look at the evolution of human characteristics and our maladaptation to the modern environment: why humans have back pain, anxiety, fever, vomiting, dystocia in females, etc. We will address why women experience menstruation and how modern medicine can circumvent monthly massive bleeding. We will also discuss how human genes have evolved to adapt to extreme environments including high altitudes, cold climates, high lactose foods, and high arsenic water. The impact of jet lag and the biological clock on disease treatment will be dealt with, together with the relationship between human compassion and oxytocin. We will then introduce the evolution of human diseases, namely, the relationship between evolution and acute infectious diseases, including the spread of the smallpox virus, the relationship between the medieval Black Death and modern HIV resistance, the relationship between sickle cell anemia and malaria infection, and why the new coronavirus is not man-made. We will further discuss the relationship between evolution and chronic diseases, including our increased risk of diabetes and why many modern people are obese, as well as the increasing proportions of modern women suffering from breast, uterine, and ovarian cancer. From an evolutionary perspective, cancer development will be explained as somatic cell evolution inside our body, starting from cancer stem cell mutations, pre-neoplastic cells competing for nutrients and blood supply with normal cells (natural selection), these cells escaping immune surveillance (surviving predators), metastasizing (migration bottlenecks and settlement), and developing resistance against cancer therapies (artificial selection). We will then look at the application of evolutionary concepts in medical research, how to discover new hormones and receptors based on their co-evolution, and the development of bionics based on unique characteristics that have evolved in diverse organisms.

Finally, we will discuss evolution beyond biology, including the evolution of human culture, the changes in memes and language, the evolution of the trilogy of religions—Judaism, Christianity, and Islam—and the future evolution of mankind, emphasizing the application of artificial intelligence in biomedicine. We will highlight how big data algorithms predict and guide what we call free will and the prospect of where human beings will take the Earth.

This book is a bird's-eye view of the history and evolution of the human species and diseases. The author hopes that its readers, regardless of disciplinary specializations in medicine and biology, might find it of inspiration for prospective research and greater understanding—either in cutting-edge scholarship or the regular diagnosis of patients. For those not in these fields, understanding human issues from the perspective of evolution might also be an enlightenment of one's life philosophy.

Much earlier and abbreviated lecture notes related to this book first came into existence in Chinese before and during the COVID-19 lockdown in Shanghai. I would like to take this opportunity to thank Professor Yi Feng of Fudan University for reading and commenting on my earlier efforts. I would like to thank Carolyn Calpin for editing the manuscript and Ms. Wang Yicong, Xie Annann, and Feng Yinzhou for picture drawing. I would also like to thank Professor Cheng Xunjia, Dean of the School of Basic Medical Sciences of Fudan University, for supporting the Fudan course and Professor Eli Adashi, former Dean at Brown University School of Medicine, for writing the Foreword. Finally, I must also thank Lily Hsueh, my beloved wife and intellectual companion of half a century, herself an esteemed fiction writer of more than two dozen creative works, for being the tireless listener of my first musings and the critical reader of my first drafts.

CHAPTER 1

DAWN: DARWIN'S THEORY OF EVOLUTION AND THE ORIGIN OF SPECIES

The biggest breakthrough in biology in the 19th century was Darwin's theory of evolution. *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races* (*Origin of Species*) by Charles Robert Darwin (1809–1882) (Fig. 1-1) was published on November 24, 1859. This book emphasizes the role of natural selection in biological evolution and is the most important and controversial work of the 19th century. Later, Darwin published two more books, *The Descent of Man, and Selection in Relation to Sex* and *The Expression of the Emotions in Man and Animals*.

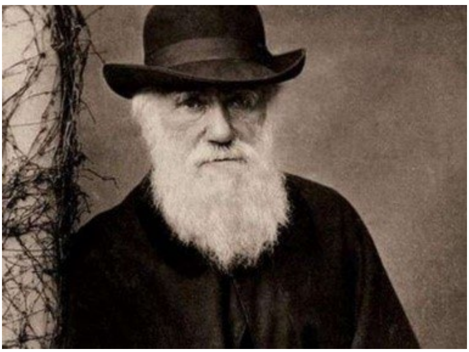
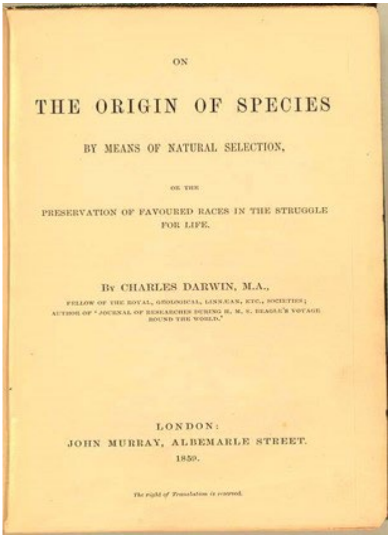


Fig. 1-1 Charles R. Darwin

**Unless otherwise credited, all illustrations in this book are either in the public domain or commissioned.*

Thomas Henry Huxley (1825–1895), a famous British naturalist, biologist, and educator, was a staunch follower of Darwin. After Darwin published *Origin of Species* (Fig. 1-2), Huxley did his utmost to spread the evolution theory and was the first scholar to raise the issue of the origin of mankind. He is the author of *Evidence as to Man's Place in Nature* and *Evolution and Ethics, and Other Essays*, which elaborated on Darwin's theory of evolution and human ethics, respectively.


ON

THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

PRESERVATION OF FAVOURED RACES IN THE STRUGGLE FOR LIFE.

BY CHARLES DARWIN, M.A.,

FELLOW OF THE ROYAL, GEOLOGICAL, LINNÆAN, ETC., SOCIETIES;
AUTHOR OF 'JOURNAL OF RESEARCHES DURING H. M. S. BEAGLE'S VOYAGE ROUND THE WORLD.'

LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1859.

The right of Translation is reserved.

Fig. 1-2 Book cover: On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races

1.1 Darwin's *Beagle* Journey (1831–1836)

In 1831, the 22-year-old Darwin followed Captain Robert Fitzroy (1805–1865) aboard the *Beagle* as a biologist. Starting from England, he crossed the Atlantic, traveled all over the South American continent and its coasts, voyaged deep into the South Pacific, and went as far as the Indian Ocean in five years (Fig. 1-3). While journeying across this wide range of longitudes and latitudes, he experienced the rich and variable natural and humanistic conditions: volcanoes, earthquakes, tropical rain forests, fossils, tsunamis, unfamiliar peoples, and different social systems. In addition, his life on board the ship, his gathering and hunting, his almost philosophical bioscience wisdom, and the trajectory of species origin and evolution were all recorded in his diary. Many of Darwin’s written materials and exquisite drawings were both intellectual and literary masterpieces. After the journey, he spent nearly 30 years combing through and summarizing the notes before expounding the theory of biological evolution.

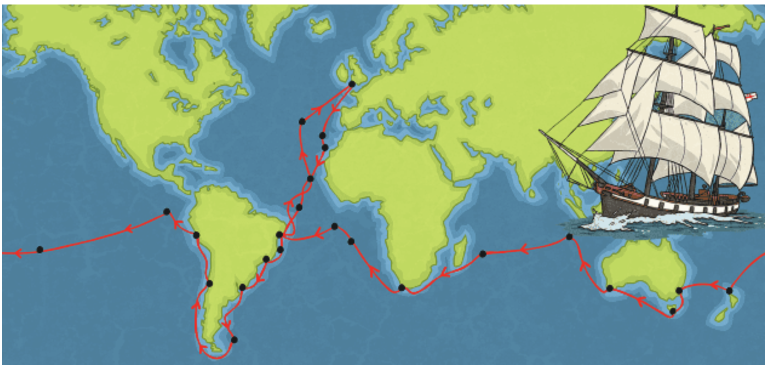


Fig. 1-3 Darwin’s Beagle *journey*

When Darwin published *Origin of Species* in 1859, he used this famous opening statement: “When on board HMS *Beagle*, as naturalist, I was much struck with certain facts.” On some islands near the west coast of South America, he found that the birds on each island seemed to be of different species, with beaks that were unique in shape and function (Fig. 1-4). Upon observing this phenomenon, he contemplated: Why are the birds on each island similar, but not exactly the same? Could these birds be adapted to the local environment on each island where they live? The small islands formed by volcanic eruptions are geologically young, and the birds on individual islands are very similar to those on the continent of South America. Could the birds on the South American continent be blown to different islands by hurricanes? To adapt to the new environment on individual islands, did they need to eat different foods to survive?

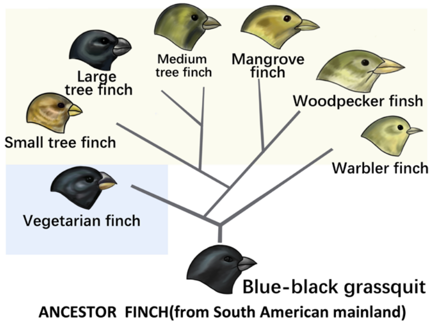


Fig. 1-4 Tree of life of Darwin's finches

Subsequently, they developed different beaks, and after several generations of reproduction, they became new, distinct species. As a result, the beaks of the offspring of the birds on each island are different. Are new species formed in this way? The logical conclusion is: Organisms can adapt to the environment and evolve new species.

At that time, people in the West believed in God's creation as written in the Bible. This meant that all species in the world should be permanent and unchangeable. Although Darwin was stunned by his discoveries, he did not dare to challenge religious authority and did not immediately publish his earth-shaking theory. It took nearly 30 years to collect more evidence and data before publishing *Origin of Species*.

1.2 The Origin of Species

Darwin drew a tree diagram (Fig. 1-5) and wrote in *Origin of Species*: "I am fully convinced that species are not immutable; but that those belonging to what are called the same genera are lineal descendants of some other and generally extinct species. … Furthermore, I am convinced that Natural Selection has been the most important, but not the exclusive, means of modification."

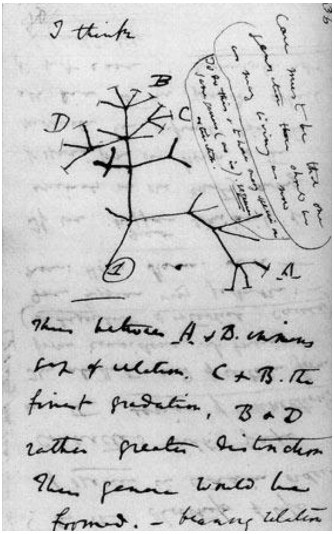


Fig. 1-5 Darwin's notes on the tree of life

Numerous scientific discoveries have been made by more than one individual. Darwin began to formulate his natural selection theory in the late 1830s. He worked silently for more than 30 years without publication. During that same period, the British naturalist Alfred Russel Wallace (1823–1913) went to the Malay Islands to collect specimens and proposed the "Wallace Line." Wallace pointed out that the bird populations on each island were different, and a deep ocean trench formed a dividing line to isolate the animal populations of Southeast Asia and Australia (Fig. 1-6). He proposed the concept of natural selection in 1858 and wrote a short article about the evolution of birds like Darwin's finches and sent it to Darwin. Darwin was dumbfounded when he read the manuscript. The results of his years of research were exactly the same as Wallace's conclusions! On July 1, 1859, Wallace and Darwin's theories were read together at the Linnean Society of London. That same year, Darwin's *Origin of Species* was published.

Fig. 1-6 The "Wallace Line" separating Asian and Australian fauna

1.2.1 Survival of the fittest

Natural selection has an important basic principle, that is, the number of organisms does not match the resources necessary for survival. In 1798, Thomas Robert Malthus (1766–1834) published *An Essay on the Principle of Population* stating his ideas: natural resources are limited and increase in a linear ratio; it is impossible to increase too quickly; and biological reproduction numbers increase in a geometric ratio. When the two lines of population and resources intersect, natural selection will occur (Fig. 1-7). Not every organism is able to survive when there are too many offspring and limited resources; this is when natural selection takes place.

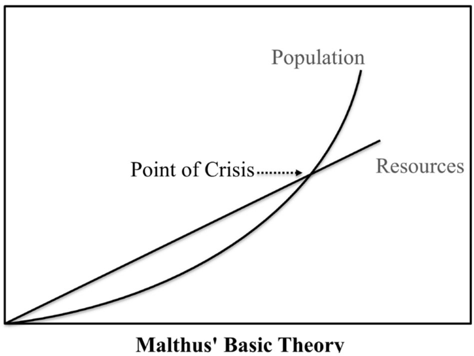


Fig. 1-7 Thomas Malthus' population growth theory

Darwin cited a phenomenon of his own time as an example: During the industrial revolution, there were smokestacks everywhere and serious environmental pollution in Britain. He found that the moths in the city were all black, while the moths seen in the cleaner countryside were white (Fig. 1-8). As moths are food for birds, white moths in the city were easily exposed against the black polluted background and eaten. In contrast, black moths could survive because of their protective colors. In the less polluted villages, white moths could survive. This provides a good example of natural selection.

Fig. 1-8 Natural selection of moths

1.2.2 Origin of species and the common ancestor

The old way of defining the term *species* includes individuals belonging to the same breeding group. This definition has several drawbacks: (1) Even for a sexual organism, it is not always testable; (2) It cannot be used for dead organisms; (3) It is not applicable to asexual organisms; (4) It is not applicable to species that are geographically isolated but genetically matched. The concept of *species* can be better understood from another angle—the common ancestor. The evolutionary tree in Fig. 1-9 shows that when tracing history along the time axis, life is a continuum, and every living thing is related. Indeed, all modern living organisms have a common ancestor. From this perspective, the characteristics of human beings that have changed due to adaptation to their local environments during evolution are reflected in living people distributed all over the world. In modern times, all humans in the world are related; in the grand picture, all living things in the world are blood relatives.

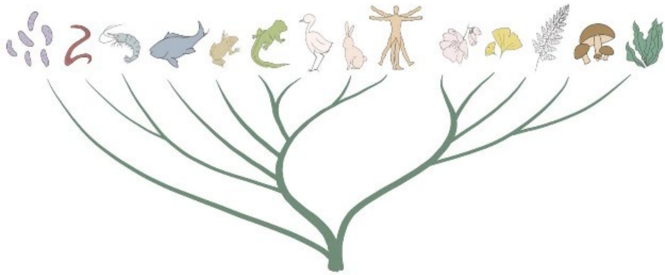


Fig. 1-9 Tree of life of diverse animals

In *Origin of Species* Darwin said, "In short, we shall have to treat species in the same manner as those naturalists treat genera, who admit that genera are merely artificial combinations made for convenience. This may not be a cheering prospect; but we shall at least be freed from the vain search for the undiscovered and undiscoverable essence of the term species." From this we can determine that monkeys are not our ancestors, but monkeys and humans have a common ancestor. We also have a common ancestor with vegetables and fruits. One just needs to trace back far enough.

1.2.3 Reproductive isolation and geographic isolation generate new species

How are new species generated? The narrow definition of species is a group of animals or plants that can mate and produce offspring. Two animals belonging to different species are unlikely to mate, and even if they do, their offspring will be sterile and will not have offspring. As shown in Fig. 1-10, the researchers used fruit flies for their experiments. Fruit flies of the same species were randomly divided into two groups, one group was fed maltose (yellow), and the other group was fed starch (red). After many generations, it was discovered that the starch-eating fruit flies (red to red) could mate, and maltose-eating fruit flies (yellow to yellow) could mate. However, red fruit flies and yellow fruit flies could not mate. In this way, new species were formed. After many generations of reproductive isolation, offspring of the original species formed two new species. This incompatibility is caused by a conflict between the specific genes carried by one species with the genes of another species.

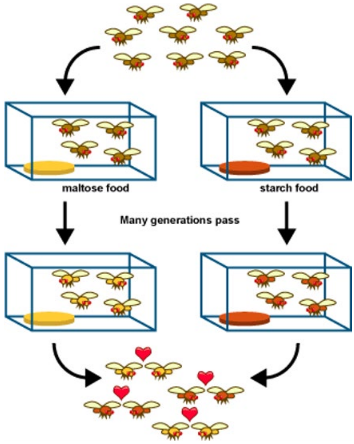


Fig. 1-2 Evolution of sub-species of fruit flies on different diets

Similarly, as shown in Fig. 1-11, the North American spotted owl and the Mexican spotted owl look exactly the same, but due to regional isolation, they can no longer mate. This is an example of geographical isolation leading to new species.

Fig. 1-3 Evolution of separate owl species due to geographical separation

The most interesting evidence for the origin of new species is the ring species. The map (Fig. 1-12) shows A, B, C, D, E, F, G, and H types of birds living in different locations ranging from Tibet and throughout China to Siberia and throughout Russia. These birds were collected and monitored by scientists. The birds look the same, but studies have found that there are two migratory routes for birds living in Tibet: one migratory route was from A to B to C all the way to the northwest, while the other birds migrated from A to F and G to the northeast.

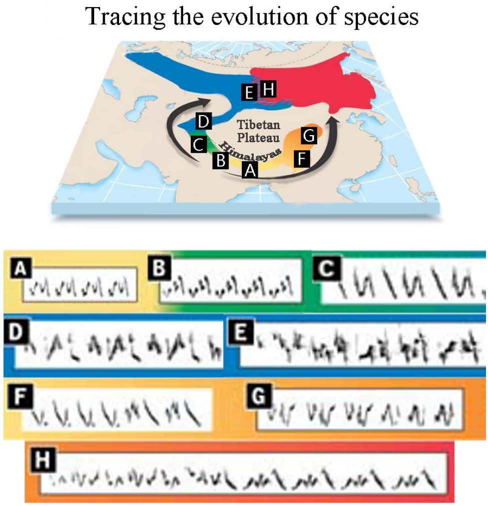


Fig. 1-12 Evolution of separate ring species of birds due to differences in mating calls. Modified from https://www.sfgate.com/news/article/Evolving-Before-Our-Eyes-Songbirds-and-2938427.php

The neighboring birds along the routes could mate with each other at the beginning of the migration routes. However, when they finally reached Mongolia (E) and Siberia (H), the two types of birds, H and E, could no longer mate. Interestingly, researchers have found that the main reason they could not mate was that their mating calls had become different. As the birds rely on their calls to find mates during courtship, once the tone and frequency of the calls of the E and H birds became significantly different, they could no longer mate with each other, thus forming two new species.

Due to geographical isolation, camels evolved into llamas in South America. The number of chromosomes in these two camel species is still the same, and camels and llamas can still produce offspring if mating were to occur. However, humans often breed new species artificially. The offspring of a lion and a tiger are called ligers, and donkeys and horses give birth to mules. These man-made new species are unable to continue to mate and propagate naturally.

An extreme hybrid formation was demonstrated in 2020. Researchers used the sperm of the American paddlefish (*Polyodon spathula*) to activate the Russian sturgeon (*Acipenser gueldenstaedtii*) egg to generate parthenogenesis (female only) embryos. This technology is also called gynogenesis, that is, the sperm only plays the role of activating the eggs; its nucleus does not participate in the development of the embryo. These two species of fish evolved into two groups as early as 180 million years ago. Russian sturgeon belongs to the Acipenseridae family and is a functional tetraploid organism, whereas the American paddlefish belongs to the Polyodontidae family and is a functional diploid organism. However, the results of the study were unexpected: The eggs developed successfully after fertilization by the sperm and produced two offspring with differences in the number of chromosomes (Figure 1-13)—the triploid hybrid and the pentaploid hybrid, which have some characteristics of both the American paddlefish and the Russian sturgeon. The successful hybridization of the two species may be the result of genome duplication and the slow evolution of sturgeons.

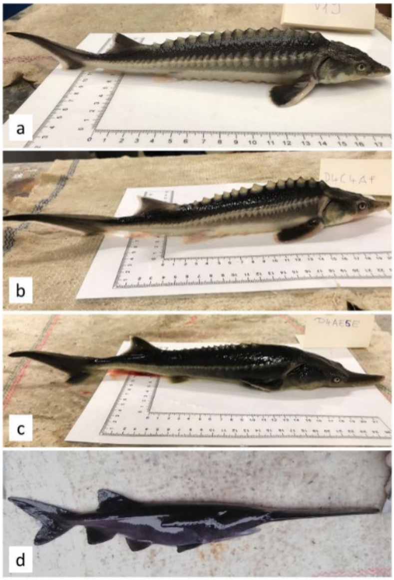
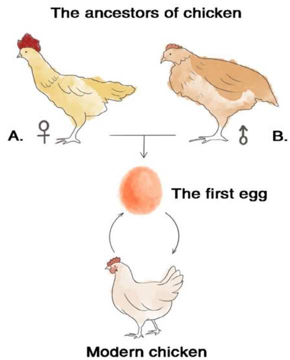


Fig. 1-13 Artificial breeding of hybrid sturgeons: a. sturgeon, b. paddlefish, c. triploid hybrid. d. pentaploid hybrid. Kaidy et al. Genes *2020, 11, 753*

1.2.4 Accumulation of small mutations allowed the evolution of new species

We can ask an interesting evolutionary question: Which came first, the chicken or the egg? From the simplest point of view, there were many oviparous creatures, such as dinosaurs, in the world hundreds of millions of years ago. They reproduced by laying eggs, so there were many biological *eggs*, but there was no such thing as a *chicken* at that time; this means that *eggs* (belonging to other organisms rather than chickens) came before *chickens* (Fig. 1-14). Of course, this is almost a word game.



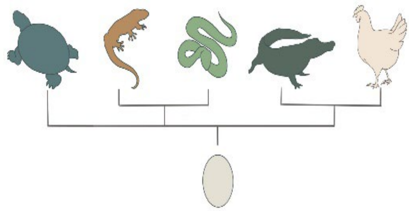


Fig. 1-14 "Chicken or egg" puzzle: answer 1

Fig. 1-15 "Chicken or egg" puzzle: answer 2

We can also look at this evolutionary problem from another perspective by using a narrower definition (Fig. 1-15). Here, *chicken* refers to modern domestic chickens, and *egg* refers to eggs that can hatch the former. It must be clearly stated that there are differences between the parent and the offspring. This phenomenon is due to mutation in the germ cells, that is, the animal and its eggs are not genetically identical if mutation took place in germ cells. However, the genes of an egg and the chick breaking the shell are the same. In terms of evolution, there may be two different chicken ancestors. After mating, they derived a genetically mutated (fertilized) egg, from which modern domestic chickens were hatched. Therefore, the answer is still the egg came before the chicken.

1.3 Does Evolution Represent Progressive Change?

1.3.1 A common ancestor

There are still misconceptions about evolution. The general idea is that most living things are low-level creatures, and human beings are the highest thanks to their progress up the ladder of advancement. In fact, human beings are different from other creatures because we have adapted to different environmental conditions. All living things have evolved from a common ancestor over hundreds of millions of years. Natural selection eliminates individuals who are not adapted to a specific environment. There are many organisms (such as fungi, sharks, etc.) that have hardly changed over time—they are not progressing up the ladder of advancement. Other organisms have undergone tremendous changes, but they have not become *better*. What was *better* a million years ago may no longer be *better* today. Adaptation is related to the environment, not to progress. Natural selection is the simple result of mutation, survival of the fittest, and inheritance. It is without a specific goal or conscious purpose of the creator. It is not progress through effort. Natural selection is not a panacea and does not produce perfection. If your genes are adequately adapted to the environment, you will be able to pass them on from generation to generation.

From a macro perspective, intelligent humans must be more *evolved* than bacteria. But in a future world where the earth is extremely warm, humans may become extinct while bacteria are able to survive. Just like the major catastrophe of a comet hitting the earth in the Cretaceous period, the most highly *evolved* dinosaurs died out, while some small, mouse-like mammals survived and became our ancestors.

Some people mistakenly think that humans evolved from monkeys, and therefore do not believe the theory of evolution. We simply have a shared ancestor with monkeys and have adapted to different environments. Natural selection will eliminate individuals who are unsuitable in a particular environment. In our modern environment, the creatures that can survive and continue to exist are organisms that have undergone minor changes. Because evolution has no purpose and no goal, it is not about becoming *better*, nor do the organisms have any intention to change. As long as genes can be passed down from generation to generation, organisms can survive. In the following chapters, we will discuss many diseases of modern humans that are caused by rapid environmental changes. The speed of our own genetic change cannot keep up, resulting in the human body's maladaptation or "out-of-step" adaptation.

Back to Darwin's story at the beginning of the chapter. On the different islands of the Galapagos, Darwin saw different types of finches, with their beaks exhibiting unique shapes and sizes. Rosemary Grant (1936–) and Peter Grant (1936–) went to the archipelago originally visited by Darwin to mark individual finches on different islands and tracked their evolution for 20 years. Jonathan Weiner (1953–) wrote *The Beak of the Finch: A Story of Evolution in Our Time* to detail the research process of the Grants. The finches on different islands have different beaks. Some are very hard and can be used to peck different types of bark; some finches can peck small seeds and fruits; some can only eat from flowers. Subsequent studies have found that minor genetic differences of BMP4 (bone morphogenetic protein 4) and CaM (calmodulin) genes could explain all the phenotypic changes of the finches' beaks. Due to the limited evolution time, there were no changes in the sequences of the genes encoding these proteins, but there were mutations in the promoter region of these genes. It is easy for changes in the promoter region to occur, buy they do not affect animal survival. However, they can regulate the expression timing and intensity of genes during embryonic development. The model involving BMP4 and CaM explains the development of the slender and deep/wide beaks of different finch species (Fig. 1-16). A large part of evolutionary innovation occurs in non-coding sequences, which can fine-tune the expression of specific genes.

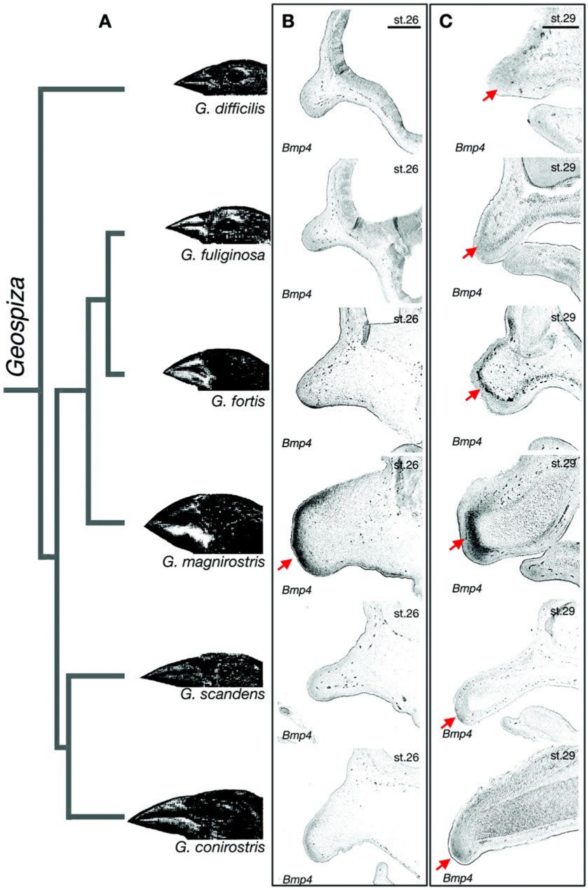


Fig. 1-16 Evolution of unique beaks in Darwin's finch species due to diverse BMP4 and CaM expression patterns. Science 305(5689):1462-5 2004

1.3.2 Lamarck's theory of use and disuse

French naturalist Jean-Baptiste Lamarck (1744–1829) used giraffes as an example to illustrate evolution. He believed that the extra neck length obtained by giraffes often stretching their necks (use) might be passed on to their offspring. Lamarck's giraffe theory was ridiculed by other biologists