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Genetics and Epigenetics of Immortality from Bacteria to Humans

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Abstract

In humans the search for immortality became concretized by 6,000 B.C. leading to the building of large tombs and statues to immortalize the dead. This refusal to accept death is not limited to *Homo sapiens*. It occurs already in bacteria, extends to invertebrates and vertebrates, and includes even plants which avoid death by activating defense genes.

It turns out that consciousness is an obligatory prerequisite of death refusal. Experiments in single cell organisms (protozoa) revealed that a minimal memory of a previous attack was a prerequisite to initiate active defense. Already in plants consciousness is directly connected with the expectation of danger. They get advanced information from volatile compounds released from other plants that elicit their defense against insects. Consciousness is also not connected with larger brains, as disclosed by a comparison of the number of neurons in birds and apes.

Cloning is a natural form of ensuring immortality, which has been used by plants and animals before humans appeared on the planet. Cloning in humans was considered in the 1930s suggesting the cloning of Einstein. This procedure is not ethical and irrelevant. Besides such an individual would not have easily survived the harassment of the mass media.

More significant is that epigenetic effects disrupt and diminish the perpetuation of immortality by changing the genome. The evidence on epigenetics is now overwhelming extending from the simple eukaryotes (yeast) to plants and humans. RNAs have an important role in modifying gene function during development and they can even be incorporated into the genome creating novel gene constellations. Immortality is becoming more difficult to achieve than expected.

Keywords: immortality, consciousness, bacteria, plants, animals, humans, number of neurons, cloning of Einstein, epigenetics

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PART 1. The Search for Immortality

1. Definition of Immortality

Immortality is: “The indefinite continuation of the mental, spiritual, or physical existence of individual human beings” (Britannica Online Encyclopedia, Duignan, 2020).

1) The “indefinite continuation” is based on the concept of infinity, that has its origin as early as Babylonian astronomy, and which dominated most of the scientific thinking in physics and biology during the 1800s and early 1900s. The universe was considered to be infinite and the number of living organisms was also considered to be of enormous proportions.

2) It has a “physical existence” *i.e.* it is a palpable event in individuals. Every phenomenon is dynamic and here may lie a contradiction.

3) The concept is restricted to “human beings”. This is also the view, characteristic of the Victorian Age, which asserted that humans were a species apart, with properties that were solely their attribute.

4) "Continuation of physical existence". This is a pivotal point. Present information, from genetics and epigenetics, reveals that the "continuation" is altered drastically during the physical transfer of gene information from generation to generation. Immortality is more restricted than it could be imagined.

Throughout the centuries, the concept changed, depending on the school of thought that dominated. The Dutch philosopher Spinoza (1632-77) refused to accept the immortality of individual persons.

Immortality has also been defined as "Exemption from death and annihilation" (Webster 1976). Here is introduced the concept of death which elucidates better this problem.

Actually, immortality, is like infinity, an abstraction of the mind. It is like our demand for perfect dice and parallel lines.

Immortality resurfaces in many ways, because it remains a deep desire of the human mind. It also turns out that immortality, consciousness and death are interlocked.

2. It Comes as a Surprise that Bacteria Already Refuse to Accept Death

With the discovery of antibiotics, such as penicillin, it was thought that infections would disappear as a result of the effective killing of bacteria. But that turned out not to be the case.

Antibiotic resistance in microorganisms became soon one of the main preoccupations of the medical profession. Following the widespread use of antibiotics, bacteria developed mechanisms that rendered them resistant to a large spectrum of medicines.

The genetic and molecular mechanisms involved became elucidated. In addition to its chromosome a bacterial cell produces *R* plasmids, small circular segments of DNA. These carry resistance genes which can be transferred between bacteria by: conjugation (transfer of DNA between two bacteria in physical contact) and transformation (the acquisition of new genes by the uptake of naked DNA). Once acquired, resistance genes are not easily lost and become spread in the population.

Multidrug resistance has been demonstrated in *Escherichia coli*, *Salmonella enterica*, *Staphylococcus aureus*, *Mycobacterium tuberculosis* and others (Dzidic *et al.* 2008).

3. Protozoa Also Refuse to Die

Protozoa are among the simplest organisms which possess a nucleus.

Trypanosoma brucei, which causes African sleeping sickness, counteracts effectively the chemicals used to combat it. The messenger RNAs produced from mitochondrial genes of this parasite undergo extensive RNA editing, which allows it to change its protein coat rapidly. By continuously producing new proteins it escapes immune attack and death (van der Ploeg 1990).

Minute cellular organisms actively refuse to remain passive when attacked by chemicals.

4. Millipedes Turn into Golf Balls when in Danger

Among the invertebrates are the small millipedes (Class Diplopoda) also known as thousand-leggers. There are more than 7,500 described species (Barnes 1980). The body consists of trunk segments which usually bear two pairs of legs. Calcium salts make the surface of these segments quite hard. Their movements invoke as many as 52 legs. When attacked by predators, the millipedes protect the vulnerable ventral surface by rolling-up the trunk into a sphere that protects also the head. They become as large golf balls. Sheldrake (2020) states that "A millipede coiled up, playing dead".

5. Faking Death in Spiders

Preston—Mafham (1996) describes in detail the various solutions that spiders discovered to avoid death and which "they play to perfection". They may: (1) fake death by becoming immobile, (2) move rapidly into a corner to hide, (3) fall down from the web carrying no thread, (4) they even disguise themselves as ants.

As Crompton (1950) wrote "Almost any animal will show fight when cornered".

6. Turtles when Attacked Turn Themselves into a Box

Turtles and tortoises have a body covered by rigid plates that protect their inner organs. At the same time these are so rigid and solidly connected, that they turn the carapace into an immobile shell. However, a number of turtles have evolved non-rigid shells with varying degrees of movements found in American box turtles and Egyptian tortoises. These have acquired a hinge on the carapace which gives the animal the capacity to close the shell, with the vulnerable parts safely within, transforming the turtle into a tight box. This is a most efficient way to avoid predators (Halliday and Adler 2004).

7. Hedgehogs Roll-up with All the Spines Erect

The hedgehog is one of the oldest species of mammals. Molecular analysis suggests that by the end of the Miocene spiny hedgehogs had undergone radiation. At present they are classified into 16 species.

The number of spines in a hedgehog is about 7,000. Wilson and Mittermeier (2018) describe their behavior in detail: "When startled hedgehogs usually lower their head and body to the ground, which covers their tail and feet, and they erect their spines. If the threat escalates to physical contact, they roll-up by using muscles to draw down the spiny dorsal skin to envelope the whole body". "Spines become erect at opposing angles to form a dense barrier of protection. When a hedgehog is rolled-up, it presents a potential predator with nothing but a puzzling spiky surface. If necessary hedgehogs can remain rolled-up for hours".

8. Plants Are not Passive Organisms but Use Different Forms of Defense

Plants can respond to a wide array of volatile compounds released from organisms such as microbes, plants and insects.

Plant defense takes even the form of an anticipation of the predation by animals, such as insects, which eat their leaves or deposit their eggs on their tissues. They get advanced information from the volatile compounds released from other damaged plants which indicate the action of herbivores.

Priming of plant defenses against plant eating is not only mediated by plant volatiles. They also respond directly to the pheromones emitted by flies. The defense against egg deposition was studied in Scots pine (*Pinus sylvestris*) trees which were exposed to the sex pheromones of the sawfly (*Diprion pini*). The result was the differential expression of several defense-related pine genes (Bittner *et al.* 2019).

9. The Demand for Longevity Genes

The human craving for immortality takes more sophisticated forms. There is an eager demand for increased longevity.

Genetics has become an industry. The most advanced tools used in biotechnology, such as *CRISPR*/Cas and transgenesis are now employed to isolate and eliminate genes connected with disease, as well as to add genes with potential health benefits related to aging.

The discovery of long-lived genetic mutants has demonstrated that aging is a genetically regulated process. Single cell organisms (yeast), worms (*C. elegans*), insects (*Drosophila*), fishes (killifish) and the mouse, have been investigated. The experiments led to the isolation and sequencing of genes that modulate life span. Upon genome assembly 497 genes were identified which included those associated with longevity in humans. This work has been carried out by different research groups that also found genomic regions enriched for these genes (Lakhina and Murphy 2015).

10. Humans Concretize their Refusal to Accept Death

The human refusal to accept death did not become concretized in the earlier period of the transition of the great apes into hominids (6 million years ago). Even after the species Homo sapiens populated the planet there were no signs of death's refusal in an organized form.

The first burials, found below houses, appeared between 7,000 to 6,000 B.C. They reveal the way humans started to dispose of their dead indicating the first concern with immortality. In more recent times the deceased were equipped with objects and furnishings, to assist life in the afterworld.

Successively the living start to be represented in statuary and art, connected with their poitical power. The search for immortality became particularly well concretized in the large pyramids of Sudan and Egypt which are tombs. It also took extreme forms such as the terracotta replica of the entire army which was excavated at the site of the tomb of the Emperor of China (221 B.C.) (Scarre 2013).

Present day human societies create extensive cemeteries and these are filled, with elaborate tombs and statues of the dead, which in every way try to immortalize them.

11. Definition of Consciousness

In the *Encyclopedia Britannica* (2015, 2021) consciousness is described "As the perception of what passes in a man's own mind". The definition refers solely to human behavior, other living organisms are not even mentioned. But in an equally recent definition of consciousness Irwin (2020) emphasizes not only its "deep roots" but also its "broad distribution" across animal species.

12. Consciousness Extends to Most Living Organisms and is an Obligatory Prerequisite of Death Refusal

The evidence just described, on the refusal to accept death, discloses that several processes are involved.

1) Memory is an obligatory first component. When a *Paramecium* (Protozoa) bumps into an obstacle, it swims backward. If it gets a stimulus from the posterior end it swims more rapidly. Experiments using intracellular microelectrodes revealed that electrical charges and calcium concentration are involved in these responses. Another protozoa, *Stentor*, when mechanically disturbed, contracts the body with the aid of an internal system of microfilaments. Microelectrodes were also used in this experiment. Eckert and Randall (1978) concluded that these simple organisms had an elementary form of memory. An initial memory of an attack was a prerequisite to start active defense.

2) Griffin (1984) also pointed out that animals behave as though they expect a certain outcome at given times.

The fact that consciousness is directly connected with expectation is central. It means that organisms are aware that they must avoid a predator. Quite unexpected, but critical, is the finding that plants, are not only capable of reacting positively to danger, but also anticipate the event. They get advanced information from the volatile compounds released from other damaged plants. Their response even leads to the differential expression of several defense-related genes. The molecular memory of plant cells was also described by Baulcombe and Dean (2014).

3) The experiments in protozoans and plants demonstrate that living organisms, without possessing a brain or a nervous system, are capable of reacting positively to danger.

4) Several stages are an obligatory prerequisite to survival: (a) Repeated injury. (b) Memory based on the repetition. (c) Awareness of the event. (d) Response by modification of the genetic make-up (plants, bacteria). (e) Active defense against death.

Hence, without previous consciousness of an attack no active defense seems to be possible. Decision, which before was regarded solely as a human mental process, now emerges as a quality of the simplest cells, and it extends to complex organisms including humans.

13. Originally Consciousness Was Associated Solely with Large Brains but this Approach is Now Superseded

Sleep is a particular stage of consciousness. It has now become evident that "Sleep exists in animals without cephalized nervous system and can be influenced by non-neuronal signals, including those associated with metabolic rhythms" (Anafi *et al.* 2019).

Plants do not have neurons but can move, respond to their environment and show strong circadian rhythms. Many plants synthesize melatonin, a hormone secreted by the pineal gland which in lower vertebrates causes aggregation in pigment cells and in humans is connected with circadian rhythms. Also, animals that lack neurons altogether, such as sponges and *Tricoplax adherens* (Placozoan) have cells that secrete neuropeptides, which have direct synaptic effects and an indirect modulatory action on the nervous system. Hence, consciousness does not need to be solely dependent on the existence of a brain or even on the presence of neurons.

14. The Number of Neurons Increases with Organism Complexity

The idea that the brain was the sole source of mental activity, had its origin in the early finding that the human brain had billions of neurons. Besides, there is also an agreement, now well established, between an increase in neuron number and the increase in evolutionary complexity (Table 1).

However, an extensive study of bird and mammalian species, including apes, has revealed that the number of neurons is not the sole main factor in establishing high cognition.

Table 1: NUMBER OF NEURONS IN LIVING ORGANISMS.
Based on Polilov (2012), Olkowicz *et al*. (2016), Anafini *et al*. (2019) and Lima-de-Faria (2017, 2020).

ORGANISM	SYSTEMATIC CLASSIFICATION	NUMBER OF NEURONS	PROPERTIES
Sponges	Porifera	0	Synaptic scaffold proteins
Tricoplax adhaerens	Placozoan	0	Possibly neuropeptides
Many species	Plants	0	Synthesize melatonin. Strong circadian rhythms
Caenorhabditis elegans	Nematode worm	302	Time sleep. Lack circadian rhythms
Megaphragma mymaripenne	Insects wasp, animal with size of a protozoan	7,400	95% of neurons lose their nuclei
Drosophila	Insects Fruit fly	100,000	Circadian rhythms
Apis, sp.	Insects Bees	1 million	Nest building
Early vertebrates	Fishes, Amphibians Reptiles	Tens of millions	Nest building, Migration
From Goldcrest (songbird) to Cokatoo (parrot)	Birds	From 164 millions to 2,122 millions	Manufacture and use of tools, Migration
Most mammals	Mammals	Hundreds of millions	Nest building, Migration, Tools
Apes, Humans	Primates	Billions	Advanced tools

Table 2: NUMBER OF NEURONS IN BIRDS AND MAMMALS COMPARED TO TOTAL BRAIN MASS.
Based on data from Olkowicz *et al*. 2016.

BIRDS			MAMMALS		
SPECIES	NUMBER OF NEURONS	BRAIN MASS	SPECIES	NUMBER OF NEURONS	BRAIN MASS
Goldcrest *Regulus regulus*	164 million	0.36 g	Mouse *Mus musculus*	71 million	0.42 g
Starling *Sturnus vulgaris*	483 million	1.86 g	Rat *Rattus norvegicus*	200 million	1.80 g
Rook *Corvus fragilegus*	1,509 million	8.36 g	Marmoset *Mico melanurus*	636 million	7.87 g
Sulphur-crested Cokatoo *Cacatua galenta*	2,122 million	10.1 g	Galago *Galago* sp.	936 million	10.2 g

15. Birds' Cognitive Capacity Matches That of Apes

Birds have been found to have cognitive abilities that even surpass that of mammals. (1) Corvids (*e.g*. raven, rook) and parrots (*e.g*. macaw, cockatoo) appear to be cognitively superior to other birds, rivaling great apes in many psychological domains as demonstrated by numerous observations. (2) They manufacture and use tools. (3) Solve problems insightfully. (4) Recognize themselves in a mirror. (5) Plan for future needs. (6) Anticipate future behavior of humans and other species.

On a first inspection the architecture of the avian brain appears very different from that of mammals, but despite a lack of layered neocortex, large areas of the avian forebrain are homologous to mammalian cortex, conform to the same organizational principles, and play similar roles in higher cognitive functions. Avian brains seem to consist of small, tightly packed neurons (Olkowicz *et al*. 2016).

16. The Comparison of the Number of Neurons with Brain Mass Reveals that Birds Have Neural Densities Considerably Exceeding Those Found in Mammals

The cellular composition of the brains of 28 avian species was compared with that of several mammals including apes.

The brain of songbirds and parrots turned out to contain very large numbers of neurons, at neuronal densities far exceeding those found in mammals. Avian brains have higher packing densities than mammalian brains (Table 2).

These extra neurons are predominantly located in the forebrain. Parrots and corvids have the same or greater forebrain neuron counts, as monkeys with much larger brains. “Avian brains thus have the potential to provide much higher “cognitive power” per unit mass than do mammalian brains” (Olkowicz *et al*. 2016) (Table 3).

PART 2. Cloning is a Process which Existed Before Humans Arrived on the Planet

1. Definition of Cloning

“The term clone, coined by Herbert J. Webber, is derived from the ancient Greek word *klon*, “twig”, referring to the process whereby a new plant can be created from a twig”. And “Cloning is the process of producing individuals with identical or virtually identical DNA, either naturally or artificially. In nature, many organisms produce clones through asexual reproduction. Cloning in biotechnology refers to the process of creating clones of organisms or copies of cells or DNA fragments (molecular cloning)” (Wikipedia, edited 2020).

This definition includes statements that demand special comment.

1) Producing individuals with identical or virtually identical DNA. This is the critical component. Epigenetic results, described in the next pages, demonstrate that the identity is far from being fully maintained.

2) Cloning is a natural form of reproduction that has allowed life forms to spread for hundreds of millions of years. It is the reproduction method used by plants, fungi and bacteria.

Many horticultural plant cultivars are clones, having been derived from a single individual. Grapes represent clones that have been propagated by over two millennia. Other examples are potato, banana and tulips.

Many trees and shrubs form clonal colonies arising naturally when parts of an individual plant become detached and grow separately.

2. Plants and Animals Had Ensured Their Immortality

Asexual reproduction in animals occurs mainly in the early forms of evolution.

Hydras are Cnidarians which reproduce asexually by budding. A bud develops, as a simple evagination of the body wall, it forms tentacles and detaches from the parent becoming an independent hydra.

Regeneration is a phenomenon that leads also to immortality and which is difficult to distinguish from asexual reproduction.

Table 3: NUMBER OF NEURONS IN THE FOREBRAIN OF BIRDS AND CORTEX OF PRIMATES.
Based on data from Olkowicz *et al*. 2016. Note: The pallium is referred to as the cerebral cortex by some authors.

BIRDS **Corvids + Parrots** Forebrain			**MAMMALS** **Primates** Cortex		
SPECIES	**NUMBER OF NEURONS** pallial/cortical	**BRAIN MASS** (pallium)	**SPECIES**	**NUMBER OF NEURONS** pallial/cortical	**BRAIN MASS** (pallium)
Eurasian Jay *Garrulus glandarius*	529 millions	2.85 g	Owl Monkey *Cercopithecus hamlyni*	442 millions	10.62 g
Raven *Corvus corax*	1,204 millions	10.20 g	Capuchin monkey *Cebus* sp.	1,140 millions	39.18 g
Blue-and-yellow Macau *Anodorhynchus* sp.	1,917 millions	14.38 g	Macaque monkey *Macaca* sp.	1,710 millions	69.83 g

Regeneration has the particular property of starting in crystals (which have no genes), to expand in simple animals and in plants, but to slow down in higher vertebrates where only certain organs are likely to regenerate (Lima-de-Faria 2017, 2020).

Regeneration is due to memory at the cellular level because the original pattern is produced without external intervention. Initially in crystals it is a pure atomic process. In unicellular algae it is the release of chemicals that determines the pattern (Brachet 1974).

Flatworms (Planaria) have been an animal of choice in regeneration experiments. Any piece, about one tenth the size of an adult flatworm, will regenerate into a complete worm and the genes involved have been isolated. The Wnt3 genes induce a wave of proliferation, low levels of this gene expression cause head regeneration, whereas high levels of this ligand result in tail regeneration (Li *et al*. 2015).

In starfish and related echinoderms, 694 genes decide the ordered regrowth of organs (Purushothaman *et al*. 2015).

Plant regeneration is a general feature and takes many forms (Xu and Huang 2014). The pluripotency and totipotency of plant cells was demonstrated, as early as 1902, when a single somatic cell gave rise to a whole plant (Haberlandt 1902).

3. Cloning of Humans Was Considered Already in the 1930s

In the early days of genetics, the fly *Drosophila* was found to have giant chromosomes consisting of distinct bands which were considered to represent single genes or groups of genes. Band changes were found to result in natural mutations. P.H. Müller was an American geneticist who looked for a way to induce artificial mutations by using X-rays, demonstrating that new mutations could be produced at will by physical intervention.

At that time in Sweden, like in the USA, the United Kingdom and Germany, eugenics was not only a generally accepted procedure, but was imposed on people with lower social status. The aim was to improve the human "race" by carefully selecting parents.

Müller (who received the Nobel Prize in 1948) was also a supporter of eugenics. According to Rose and Rose (1999) he speculated on cloning Lenin and Einstein. Another geneticist, in England, J.B.S. Haldane, thought of cloning women as well. In the 1990s, and in later years, American novels and films have been based on this theme.

4. A Cloned Einstein Would Probably not Have Survived the Harrassment of the Media

The ethical implications of human cloning are extremely serious and at the same time irrelevant.

It is usually not recognized that a human being is born in a social and intellectual, as well as a historical environment that cannot be repeated. This environment is equally important, as the genetic constitution, in deciding his or her intellectual behavior.

Einstein was born in a period of revolutionary ferment that put in doubt all previous concepts, not only in science but also in society, due to the revolutionary works of Bakunin, Kropotkin, Marx, Lenin and others. Significant is that some of them lived in Switzerland like Einstein.

As Cahn (1960) describes in his biography, Albert Einstein was born in 1879 in Ulm, Bavaria, and moved later to Munich, Germany. There he was obliged to stand the intolerant and militaristic policy of Chancellor Bismarck. The result was that the family emigrated to a tolerant Switzerland.

As a child Albert was slow to talk and slower to read. In the German school he was in trouble since he refused to accept the dogmatic atmosphere imposed with "blood and iron". Important in his career was an elderly uncle who introduced him to the science of mathematics. In Switzerland he renounced his German status and became a citizen of Switzerland. Throughout his life, a violin and a sailing boat were among his sources of pleasure.

A cloned Einstein would lack all this familiar and intellectual environment. He would have no loving parents, no dedicated uncle and no land where all concepts in science and society were put into question.

A revolutionary mind, that transformed physics in its basic concepts, could only develop in a particular intellectual atmosphere.

The conclusion is inescapable. If Albert Einstein were to be cloned the new baby would have no parents, no family and no comparable society to grow in. Moreover at once he would be declared a genius, a condition that he could not in any way satisfy. Suicide was most probably the only solution in sight.

It may be recalled that one of Pablo Picasso's children committed suicide since he was expected to be a genius like his father. Jaqueline, the wife of Picasso, also committed suicide. She could not stand the pressures of the mass media.

PART 3. Epigenetics Events Disrupt and Diminish the Perpetuation of Immortality

1. Epigenetics Was Established in the 1950s but is Heralded at Present as a New Discovery—An Example of How Science is Directed by Social Interests

It was the embryologist C. H. Waddington, who, as early as 1940, coined the term epigenetics (Rieger *et al.* 1968). By the 1960s he had created the Department of Epigenetics adjacent to the Institute of Animal Genetics at the University of Edinburgh, Waddington developed his novel concept in a series of books (1940, 1957 and 1962). But geneticists continued to refuse such an approach and even blocked the publication of the results.

In the meantime the active search for the cure of cancer and diabetes, became a pressing social issue. It demanded studies, at the molecular level, which finally led to the acceptance of epigenetics. However, as late as 2014, American cytologists called epigenetics "A New Kind of Inheritance" (Skinner 2014) transforming European science into an American discovery. This is an event that continues to occur quite often, discarding ethical principles.

2. Definition of Epigenetics

The term was originally defined as the branch of biology which deals with the causal analysis of development (Rieger *et al.* 1968). Later as "The study of the chemical modification of specific genes or gene-associated proteins of an organism.

Epigenetic modifications can define how the information in genes is expressed and used by cells." "Researchers have uncovered a range of possible chemical modifications to DNA and to proteins, called histones, that associate tightly with DNA in the nucleus. These modifications can determine when or even if a given gene is expressed in a cell or an organism" (Fridovich-Keil 2017, 2020).

3. Molecular Biology Confirms Epigenetic Events and their Inheritance

At present the evidence is overwhelming:

1. DNA sequences change during development. This is not only due to spontaneous mutations and numerous chromosome rearrangements but mainly to exon-intron shuffling (the process through which new genes are generated by recombination of one or more exons of other genes) which is a widespread event in the genome (Herbert and Rich 1999). Also the methylation of DNA sequences (addition of a simple methyl group to a nucleotide) can be transient but can be permanent, when set early in the development of the organism. This turns out to be the principal type of gene modification.
2. Another permanent modification of DNA is carried by histone acetylation and phosphorylation. Also certain modifications of this protein lead to expression or repression of genes in different kinds of cells.
3. DNA is not as important as we tend to think. The rigid order that directs embryonic formation is not directed by DNA but by microRNAs that before were considered irrelevant molecules. It is these small sequences, 21 to 22 nucleotides in length, that have the road map and which charter the events that lead to the production of a specific organism. These microRNAs are transcribed from non-coding genes (Carrington and Ambros 2003).
4. Some genetic modifications are spontaneously erased, when cells reproduce, thereby precluding their inheritance but other epigenetic modifications are heritable, being passed from parents to offspring, which is referred as epigenetic inheritance (Fridowich-Keil 2017).

4. RNAs Have an Important Role in Epigenetics and Can Be Incorporated into the Genome

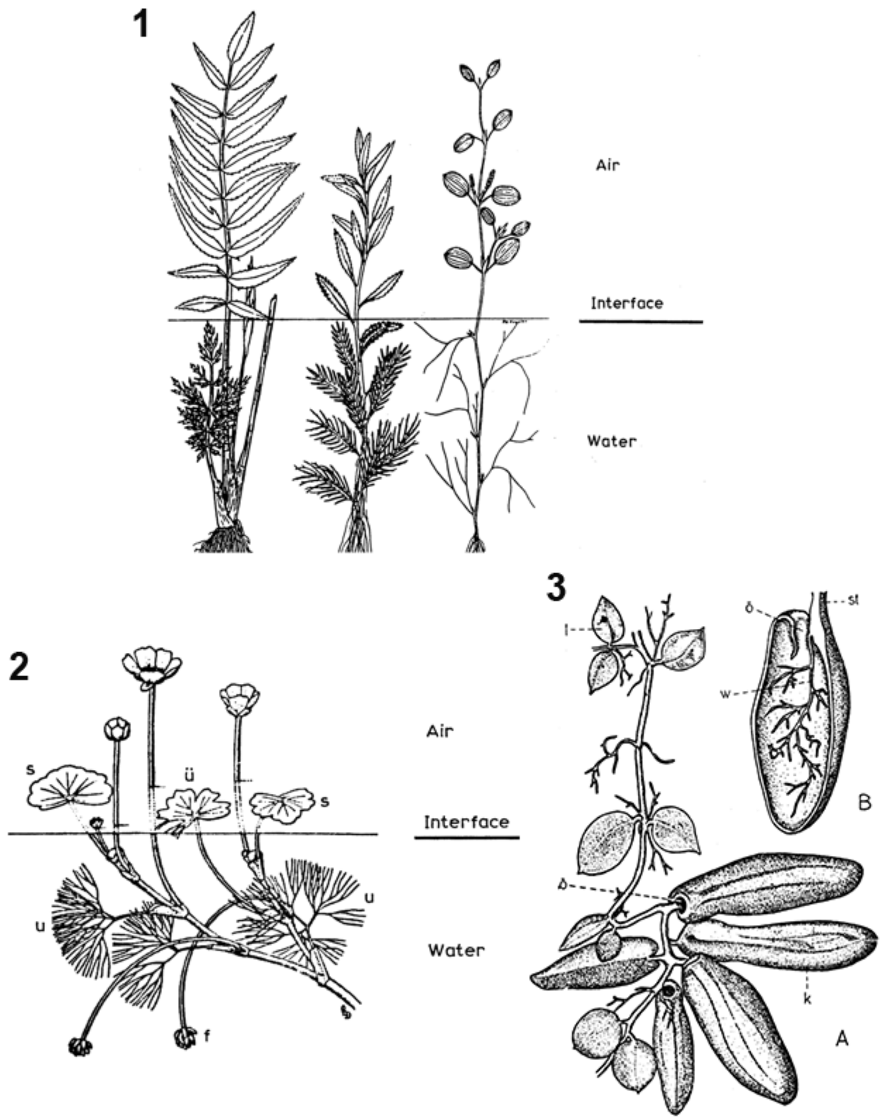
As Lehninger (1975) stated "So far as we know, living organisms normally contain no functionless components, although there are some biomolecules whose functions are not yet understood". The molecular evidence gathered since then has vindicated the validity of his statement. The entire genome in living organisms generates a myriad of non-protein-coding RNA species that participate in gene expression and its regulation leading to epigenetic events. As Ponting *et al.* (2009) put it "Eukaryotic genomes are not the simple, well-ordered substrates of gene transcription, that was once believed".

As development unfolds most nucleotides in the genome are transcribed producing a huge array of RNA molecules differing in size, abundance and protein-coding capability.

Among these are the long noncoding RNAs (larger than 200 nucleotides) that are involved in transcription regulation.

Eukaryotes use relatively little of their genome to code for proteins. Besides messenger RNA transcripts are extensively processed, by alternative splicing and RNA editing, generating many different messages from the same gene.

Significant is that this RNA pool can be incorporated into the genome over time by reverse transcription (Herbert and Rich 1999).



Figures 1-3. Fig. 1: Three aquatic flowering plants showing different leaf patterns in air and water. **Fig. 2:** Three types of leaves are formed in *Ranunculus peltatus*: submerged with many linear segments (u), transitional form with a few linear segments (ü) and the floating palmate type. **Fig. 3: (a)** The carnivorous plant *Dischidia rafflesiana* has leaves with two different functions: normal leaves appear in the upper part and leaves in the form of a pitcher are formed in the lower part of the plant. The function of the upper leaves is mainly photosynthesis, whereas the lower pitchers attract insects and digest them. **(b)** Cross section of a pitcher.

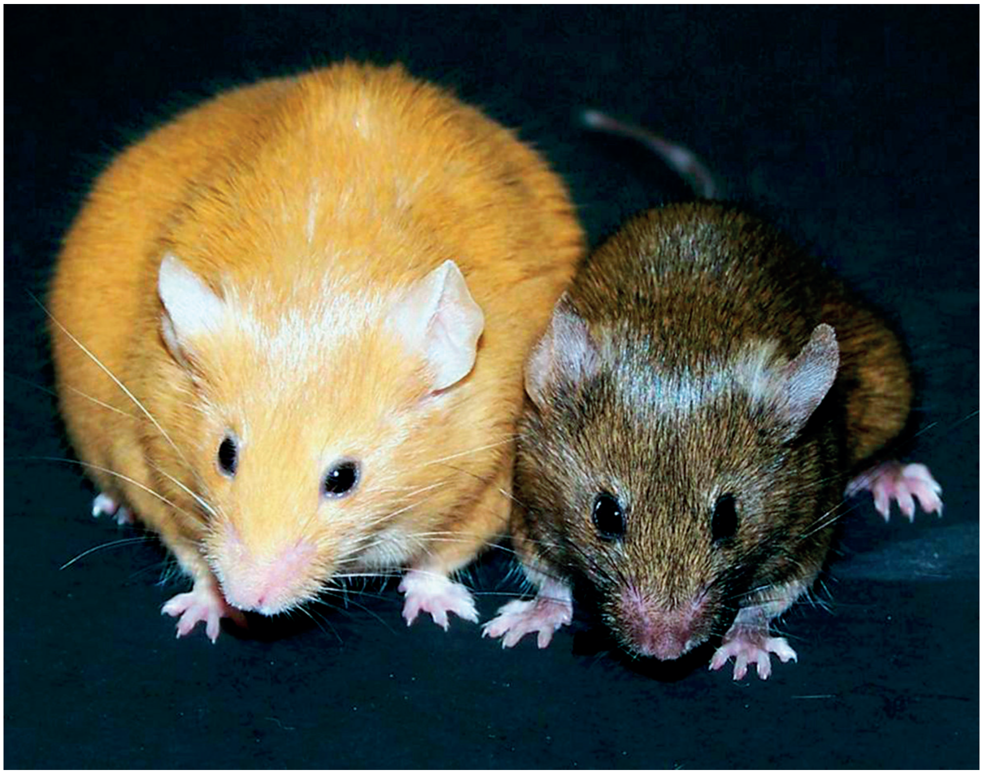


Figure 4: Agouti fat and yellow mouse (left), which functioned as a mother, at the side of its brown and skinny progeny (right). The mother received a diet rich in vitamin B12 and folic acid. This is a typical epigenetic effect since the agouti gene was switched off in the offspring which became brown.

5. Micro RNAs Affect Animal and Plant Development

Several hundreds of small RNAs and microRNAs, have been identified in animals and plants, which lead to the control of gene expression during development. The microRNAs arise from larger precursors that are transcribed from non-protein-coding genes. The precursors of these RNAs are termed *DICER* (in animals) and *DICER-LIKE 1* (in plants).

Plant microRNAs generally interact with their targets through near-perfect complementarity and direct messenger RNA target degradation. Short interfering RNAs (siRNAs) may also guide nuclear events including histone and DNA methylation, resulting in transcriptional silencing, a typical epigenetic event (Carrington and Ambros 2003).

In addition, RNA editing in plants alters the identity of nucleotides in RNA molecules, so that the information for a protein in the messenger RNA, differs from the prediction of the genomic DNA. In chloroplasts and mitochondria of flowering plants RNA editing changes C (cytidine) nucleotides to U (uridine) nucleotides. In ferns and mosses, it changes U to C.

In mitochondria there are approximately 500 editing sites and there are 40 editing sites in plastids of flowering plants (Takenaka *et al.* 2013).

6. Epigenetic Events Occur Already in the Simplest Eukaryotes

Escherichia coli (bacteria), *Saccharomyces cerevisiae* (yeast), *Caenorhabditis elegans* (worm), *Drosophila melanogaster* (fruit fly) and *Arabidopsis thaliana* (flowering plant) are the most investigated species from the genetic point of view.

Yeast is one of the simplest eukaryotic organisms and has been thoroughly investigated for decades. It turns out that it already displays epigenetic events (Allshire and Ekwall 2014). This is important because it shows that the phenomenon extends all the way from the simplest to the most complex living organisms (humans).

7. Epigenetics in Plants is a Widespread Phenomenon

The occurrence of different leaf patterns within the same individual plant has been described, and illustrated, for decades in botanical treatises.

Various species of aquatic plants, with shoots that are partly submerged under water and partly aerial, generally have submerged leaves that are highly dissected and thin in contrast with the thicker and entire, or only moderately lobed, aerial leaves (Figure 1). The different forms were attributed originally to environmental factors, such as

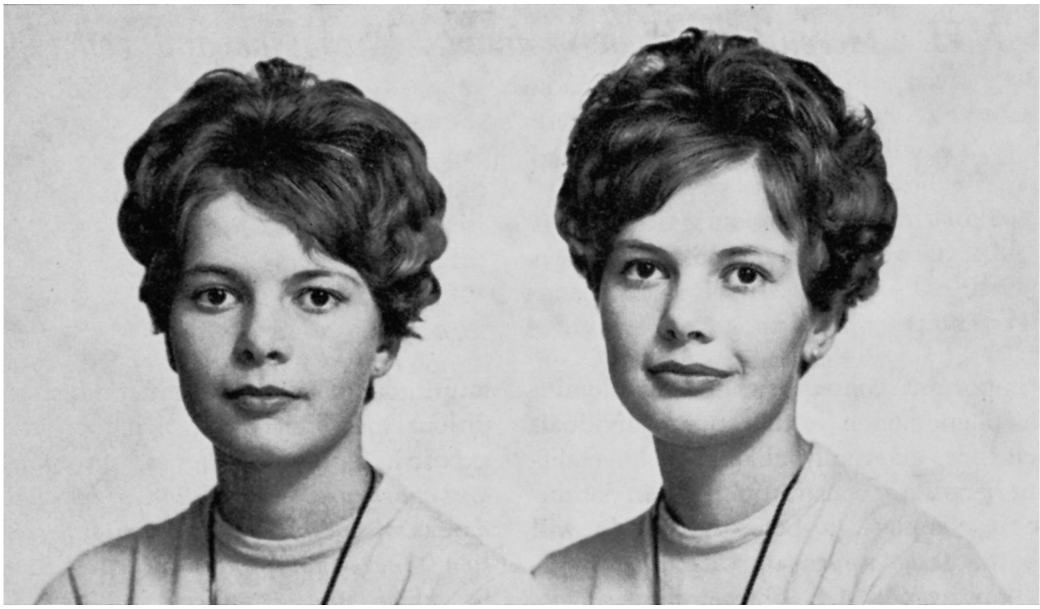


Figure 5: The identical twins Monica and Gerd. Monica is left-handed and has the hair to the right. Gerd is right-handed and has the hair to the left. They are mirror images of each other. Mutations in the gene Pitx2, in mice and humans, are involved in left-right symmetry.

temperature, light and humidity, but Greulach (1973) already pointed out that "environmental factors are of secondary importance" in bringing about this differences. Obviously, the environment has an effect but this remains to be investigated at the molecular level.

Another classical example is displayed by *Ranunculus peltatus*. Three different types of leaves occur in this partly aquatic species of flowering plants: (1) submerged leaves with many linear segments , (2) transitional forms with few linear segments and (3) floating leaves which are palmate (Figure 2).

Hedera (ivy) shows also two types of leaves. Experiments demonstrate clearly that it is an epigenetic phenomenon connected with gene imprinting. The juvenile leaves are lobed, but the mature leaves, that appear in the reproductive phase, are entire. Cuttings of the ivy from a flowering branch will produce only the entire pattern. The lobed form only reappears when the plant is propagated by seed, i.e, through sexual reproduction (Denffer *et al.* 1976). Cell memory and its erasing is now well documented at the cellular level (Gehring 1985).

8. In Carnivorous Plants Epigenetics Changes not Only Affects Structure but Also Function

Within the same plant, carnivorous leaves emerge at the side of non-carnivorous ones by change in gene expression. This epigenetic event is a general phenomenon in plants (Matzke *et al.* 2015) and is mainly due to RNA-directed methylation of DNA (Herbert 2004). Examples are: *Genlisia* has non-carnivorous flat green leaves above ground and distinct subterranean carnivorous leaves which form corkscrew traps. In *Triphyophyllum* three distinct types of leaves appear during development: (1) juvenile, non-carnivorous leaves, (2) carnivorous leaves and (3) mature stage with no carnivory but flowering. Two types of leaves occur in other genera: *Sarracenia*, *Nepenthes*, *Drosera*, *Pinguicula* and *Utricularia* (Figure 3). Not less than 8 genera of carnivorous plants produce leaves of different types within the same individual plant (McPherson 2010).

9. Mice Have Been the Animals of Choice in Studying Mammalian Epigenetics and its Relation to the Environment

Mice carrying the "Agouti" variant of a gene are genetically identical. However, depending on what their mother ate during pregnancy, the offspring can differ dramatically: they can be brown or skinny with the mutation switched off, or they can be fat, yellow, and prone to obesity and diabetes, when the gene is on. The switch comes from the mother's environment which affects her genome and changes the fate of the offspring.

The pregnant yellow mother was fed a diet rich in nutrients such as folic acid and vitamin B12. The "Agouti" gene was switched off in the pups which are consequently brown and thin; not fat and yellow. This is considered a typical case of epigenetics (Figure 4) (Chong *et al.* 2007, Wolff *et al.* 2007).

Since then mice have been studied extensively to better define this type of inheritance at the molecular level showing that DNA methylation and histone acetylation are the cause of this process (Blewitt and Whitelaw 2013).

10. Genetic Similarities Between Mice and Humans

Mice became a model in many experiments performed to elucidate epigenetics in humans.

The "Mouse Genome Database" facilitated the comparison of mouse results as a model for human biology as well as disease (Eppig *et al.* 2015). It explored gene — phenotype — disease relationships between humans and the mouse but also microRNA interactions.

The two species are closely related not only anatomically and physiologically but their gene numbers and functions are also similar. In the mouse, the number of genes with protein functions are 24,613; of these 17,055 are mouse genes with human orthologs (i.e. homologous genes in different species that arose from a single gene in the last common ancestor of these species). The number of human diseases with one or more mouse models was found to be 1,323 which reveals their close relationship.

11. Epigenetics in Humans

Mice and rats have been used in the search for epigenetic events in humans (Morgan and Whitelaw 2008).

Genes termed *metastable epialleles* have been identified in the mouse which are responsible for color variegation. This is due to cells of the same type that do not express the gene. Examples of this phenomenon are *agouti viable yellow* and the *axin*-fused. Their epigenetic behavior is due to the insertion of a transposon silencing the promoter. DNA methylation at this promoter correlates with silencing. As mentioned above changes in the mother's diet during pregnancy alter the proportion of yellow mice within a litter. Methyl donors including betaine, methionine and folic acid result in a shift in the color of their offspring away from yellow and towards *agouti*.

In humans, a number of reports describe similar effects, and *metastable epialleles* were also identified, which are good candidates for transgenerational inheritance in this species.

Recent studies in humans, reveal that several diseases result from the disruption of the epigenetic state which can also be inherited across generations. These diseases are: decreased mental capacity, obesity and colorectal cancer in which aberrant methylation of DNA is involved (known as a main source of epigenetic modifications).

These mutations are difficult to establish in humans, but there is evidence that choline, which is an essential nutrient involved in epigenetic modulation of gene expression together with other methyl donors, has been found to have a role in carcinogenesis.

The result is that the US Food and Drug Administration, as well as similar European Authorities, recommended levels for adequate intake of choline (Zeisel 2017)

Psychiatric disorders, like drug and alcohol dependence, also conform with patterns of epigenetic changes (Wong *et al.* 2011).

For geneticists symmetries were considered a curiosity belonging to the domain of physics. For molecular biologists they continue to be of marginal significance since they cannot be explained by selection.

Müntzing (1961) published a figure of two Swedish twins Monica and Gerd. Monica was left-handed and had the forelock to the right. Gerd was right-handed and had the forelock to the left (Figure 5). He described them as mirror images of each other, but this change in symmetry, occurring within the same genetic constitution, was a problem foreign to the constancy of gene action.

Since then it has been found that: (1) Symmetries are a phenomenon that is inherent to matter, occurring already in elementary particles such as the neutrino. (2) Left-handed and right-handed structures occur in galaxies, carbon atoms, quartz crystals, amino acids, DNA configurations, flowers, snails and humans (Lima-de-Faria 1995). (3) Recently, the reversal of left-right forms in mice has been related to a mutation of a gene that controls embryonic polarity (Yokoyama *et al.* 1993). The homeotic genes are also involved in the emergence of bilateral symmetry in the chicken, the mouse and humans (Yokouchi *et al.* 1991) and Ryan *et al.* (1998) found that the transcription factor *Pitx2*, which has a homologue in humans, also participates in left-right symmetry.

At present the patterns of Monica and Gerd indicate an epigenetic effect that resulted from mutations in genes directing embryonic development.

Conclusion

The evidence available at present on epigenetic effects, which extends from simple organisms, to plants and higher vertebrates (including humans), is overwhelming.

But we are far from knowing the main events participating in this process: (1) Knowledge is lacking of the own evolution of DNA as well as the type of mutations that result from this event. (2) Also the own evolution of RNA needs to be elucidated, since it is a major factor, due to RNA editing. (3) The molecular cascades that follow the alterations in DNA and RNA, are not known. (4) Neither are known the atoms which are responsible for deciding the final pattern.

These serious limitations on the atom behavior of simple and complex macromolecules are being elucidated by research carried out at the atomic level by the use of the large accelerators of electrons and neutrons which are now part of Lund University (Max IV and European Spallation Source) (Lima-de-Faria 2017, 2020).

Source of Figures

Figure 1. From Lima-de-Faria (1988), page 243. Originally from Greulach (1973).

Figure 2. From Lima-de-Faria (1988), page 245. Originally from Denffer *et al.* (1971).

Figure 3. From Lima-de-Faria (2017), page 37. Originally from Strasburger (1943).

Figure 4. From Wikipedia commons, File: Agouti Mice.jpg. 2021. CC by 3.0. Date 7 August, 2007. Source E-mailed by authors, Randy Jirtle and Dana Dolinoy.

Figure 5. From Müntzing (1961), page 54.

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