TINKERED MASTERPIECES OR MASTER TINKER

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INTRODUCTION

There is controversy about the source of biological diversity on Earth. This essay looks at the past century and a half during which time a robust idea (evolution of diversity in species by natural selection) was born, grew and developed into a complex structure of knowledge, maturing to the point at which it could understand itself far better than at the time of its birth. To be sure, new knowledge arising in the modern genome projects will again surprise and disturb us about the phenomena and mysteries of evolution and gene-based life. All that is said here about biological evolution need not intrude upon our personal views about the emergent properties of living organisms and our faiths in other realities. Montaigne, reflecting on our mysteries, said: "Man is quite insane. He would not know how to create a maggot, and he creates gods by the dozen".

II. PROXIMATE AND ULTIMATE EVENTS

[The reader is referred to various sources for fuller exposition]*.

Variation among species has proximate and ultimate sources. Darwin[1]• and Wallace[2] surmised the *proximate* force to be natural selection but they could not know on what aspect of the organism this force was acting. Darwin's genius encompassed a bottom-up anarchic but ordered view of life evolving by cumulative integrated assembly of minute incremental changes over long stretches of time. He saw natural selection as a

* They are listed after the text.

• Annotations are Numbered and appear in sequence. A *Dictionary of Genetics* (5th ed. RC King, WD Stansfield. OUP 1997) has been a useful source.

[1] *Charles R. Darwin* (1809-1882)

[2] *Alfred Russell Wallace* (1823-1913)
Darwin and Wallace independently conceived the role of natural selection in the origin of species (1858)

creative force. He saw all life to be connected over the extended time of evolution; human life was not exempt from the evolutionary process.

Sober's synthesis of prevailing ideas in the late 20th century (Sober 1984), recognizes that the process of natural selection acts on a phenotype (which is now allocated primarily to the proteome[3]); hence the corresponding interest in any measurement of selection at work to improve the reproductive success of the individuals in a species.

Darwin and Wallace had no knowledge of the *ultimate* source of variation of species; they did not know about the "life code" behind the process; (the latter was initially surmised by Schrödinger[4] in his famous lectures delivered in 1943). Neither Darwin or Wallace knew anything about the materialistic Mendelian elements of inheritance (now called genes); and no one at the time had any insight on the additional concept of *mutation* in the "genetic code". Again, Sober goes to the heart of things to identify the object selected by the process of natural selection; it is the gene encoding the particular protein phenotype; mutations that change phenotype are the *ultimate source* of the changed interaction between organism and experience.

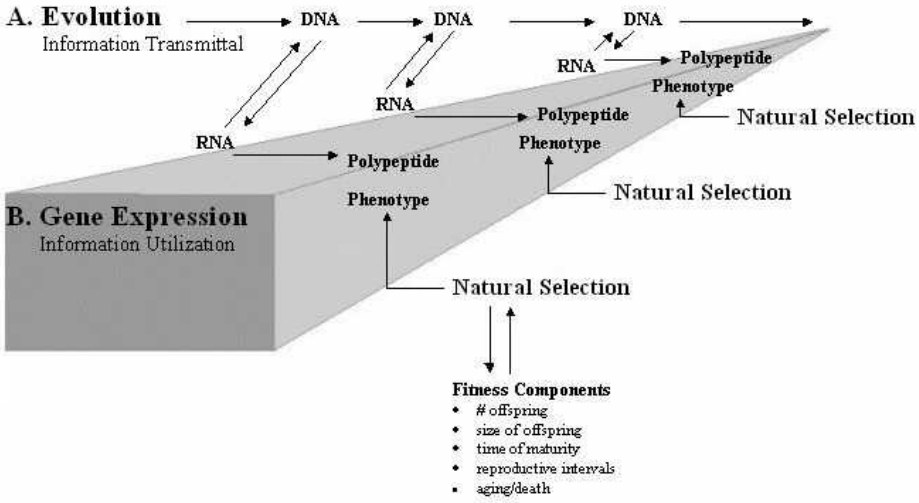
Hence the humble wisdom that organisms are only vehicles for

[3] Proteome: a new term to describe the protein counterpart of the genome.

[4] Erwin Schrödinger (1887-1961) was the author of an influential set of lectures "*What is Life? The Physical Aspect of the Living Cell"* (Cambridge, 1944). He left Nazi Germany to take up a post at Trinity College, Dublin where the lectures were given.

passing on genes (Dawkins 1995), and the more successful the organism is at passing on its genes the more successful the "selfish" gene will be at getting itself copied and distributed into the population (Dawkins 1989). While writing about this concept, Dawkins went even further to suggest that memes and brains are the replicable counterparts of genes and bodies (see Chapter 11 in Dawkins (1989)).

These ideas translate into a pair of simple biological paradigms: one is dedicated to genetic information transmittal (with either fidelity or change (mutation)); the other leads to information utilization (DNA makes RNA makes protein …. Makes phenotype) (Figure). The fundamental concepts of biology reside in these two paradigms.



Today, these paradigms invoke ambiguous responses in ourselves. Mutation is necessary for evolution of biological diversity (good) yet it can be a cause of disease in the living

organism (bad). Therefore could evolution ever have happened by this materialistic process particularly if it is harmful to individuals. Furthermore, it has always been difficult to understand the inherited complexity behind the making of phenotype. Whereas one can speculate about how and why inheritance of genetic variation is either *dominant* or *recessive*[Δ], it was largely through biochemical thinking and experimentation that answers were revealed (Kacser and Burns, 1981). In trying to answer the persistent question – "why is it that any new expressed mutation is not always a disaster", it is natural in the era of the genome, and with access to the new powerful and reductive tools of molecular genetics, that there is renewed interest in the cellular mechanisms that buffer mutation effects (Hartman et al. 2001), that establish boundary conditions (Strohman 2002), and how they make "evolvability" possible (Kirshner and Gelhart 1988; Kirshner et al. 2000).

The remainder of this essay connects discoveries in genetics to an understanding of variation in biological phenotypes.

III. "*Nothing in biology makes sense except in the light of evolution*" The geneticist T.G. Dobzhansky[5] articulated this truth in many of his writings, and of special note, in a brief paper addressed to teachers of biology in the schools of the nation (Dobzhansky 1973). In the era of genomics, where genomes of many organisms are being sequenced and

[Δ]Definitions: A dominant allele manifests its phenotype in the heterozygote; a recessive allele is silent (masked by the paired allele) in the heterozygote's diploid genome.

[5] *TG Dobzhansky* (1900-75) proposed to Oswald Avery (see note 19) that mutation (a process) might explain a phenomenon (transformation of a phenotypic property) [see Olby 1974 (p. 189)]

interpreted, it has become apparent that the evolution of genomes, generated by the dialogue of natural selection, has produced genomic elements that are being used in the genome of *Homo Sapiens*. François Jacob[6] (1982) observed that evolution takes place by tinkering (bricollage*); and nothing in human biology will make sense without considering the historical process of evolution. Other interpretations, such as a grand Grand Design for the variety of life on Earth are either an illusion or a different form of reality. Does it matter to know what is illusion, what is reality? Humans with free will are free to choose which it is; – or perhaps both …. But remember - for every choice there is an irrevocable loss!

IV. MENDELISM IS DISCOVERED AND REDISCOVERED.

Loren Eiseley, in his historical analysis (Eiseley 1958), argues that the time was ripe in 1858 for Charles Robert Darwin and Alfred Russell Wallace to propose jointly to the Linnean Society of London that Natural Selection, over vast stretches of time, was the force behind biological evolution and the origin of species. As mentioned earlier in this essay, at the time, Darwin was ignorant of *the mechanism* of the evolutionary process (Mayr 1982) and Mendel's recent discovery of materialistic hereditary factors had eluded him (and almost everyone else). Re-discovery of Mendel's evidence in 1900[7] lead Bateson[8] to coin the word "genetics" at a time when Wilson[9] had recognized the cell to be the vehicle for phenotype, thus bypassing some of

[6] *F Jacob* (1920 -) received a Nobel Prize in 1965, which he shared with J Monod and A Lwoff, for work on the operon concept and gene regulation.

*the French word has a certain charm.

[7] *H de Vries, C Correns, and E Tschermak,* in 1900, independently discover Mendel's paper of 1866.

[8] *W Bateson* (1861 – 1926), English geneticist, promotes Mendelism and introduces a vocabulary: *genetics, allelomorph, homozygote*, etc.

[9] *EB Wilson* (1856-1939) author of the influential book *The Cell in Development and Heredity*.

[10] *MJ Schleiden* and *T Schwann* develop a Cell Theory (1838-39) in which cells have nucleii and cytoplasm; *JF Miescher* (1869) extracts nucleii from cells; in 1870 he purifies its component that will eventually be called "DNA"; in 1889 his pupil *R Altmann* names the latter "nucleic acid".

the mysteries of vitalism by anchoring biology solidly in Cell Theory. [10] Somewhat earlier, Weismann (1884) had recognized that continuity of species ("immortality") involved separate fates for germline cells and somatic cells; thus began the concept of the "disposable soma", a finite lifespan of the body and a "continuing" existence for the germline and the information it contains (see note [11]).

V. CHROMOSOMES ARE FOUND TO HOUSE HEREDITARY FACTORS

Late in the 19th century, chromosomes were recognized as the physical structures directly involved in heredity.[11] The first case describing linkage between two of Mendel's hereditary factors on chromosomes is documented in a plant (the sweet pea) in 1906. The phenomenon of physical linkage between loci harbouring Mendelian factors is next described in fine detail on the chromosomes of the fruitfly (an organism of great value for genetic research). The linkage phenomenon is shown by JBS Haldane[12] to apply to a vertebrate (the mouse, another "model" genetic organism); in the same year (1915) E.B. Wilson surmizes that the hereditary factor causing human color blindness is linked to the X chromosome. However, it was not until 1951 that linkage on a non sex (autosomal) chromosome would be demonstrated; in this case, for the Lewis and Lutheran blood groups. Only in 1968[13] would it be possible to assign the

[11] *W Flemming* shows (1879) that nuclear division involves longitudinal splitting of "chromosomes" into sister chromatids; he coins the word "chromatin". In 1882 he also coins the term "mitosis". *A Weismann* (1883) then distinguishes between the somatic cell line and germ cells; in 1887 he describes the process that will be called "meiosis". *T Boveri* (1888) recognizes individuality in the appearances of pairs of chromosomes; *W Waldeyer* (1888) provides the word "chromosome".

[12] *JBS Haldane* (1892-1964) geneticist, polymath. See JF Crow's appreciation of Haldane in: JF Crow and WF Dove. *Perspectives on Genetics. Anecdotal, Historical and Critical Commentaries, 1987-1998,* Wisconsin Univ. Press. Madison. 2000. p. 253-258.

[13] *RP Donahue* and colleagues show that segregation of Duffy blood group in his family is linked to a dominantly inherited microscopically visible secondary constriction (at an uncoiler locus) on the long arm of chromosome 1.

[14] *Wilhelm Weinberg* (1912) observes that sporadic cases of achondroplasia tend to occur in lastborn sibs; *LS Penrose* (1955) relates this to advanced paternal age and spontaneous mutation in the male gamete that has experienced many divisions.

gene for a specific blood group (Duffy) to a particular human chromosome. [How slowly are the abstract concepts joined to corresponding physical entities during these decades of genetic research!]

VI. GENES ARE MATERIALISTIC ENTITIES

The materialistic nature of human heredity is tellingly revealed when Weinberg[14] proposes that a newly considered phenomenon called "*mutation"*, (a term initially coined by deVries in 1901), is the cause of achondroplasia, a human form of short-limbed dwarfism notably celebrated in the famous painting by Velasquez known as *Las Meniñas*. In 1927, the materialistic hypothesis is further consolidated when HJ Muller[15] induces germline mutations in fruit flies by X-radiation. JBS Haldane (in 1935) calculates the spontaneous mutation rate in a human gene. Later still the fact of spontaneous mutation is unambiguously demonstrated in bacteria.[16] Accordingly, there is an inescapable conclusion that *mutation* in "genes" is a mechanism underlying variation in the inherited phenotype of any organism.

VII. GENES AS TRANSFORMING PRINCIPLES.

Evidence that Chance, in the form of Natural Selection, can change the distributions of genotypes in populations, is provided when Goldschmidt[17] studies industrial melanism in the moth in the English Midlands. The phenomenon is further described in

[15] *HJ Muller* (1890-1967): awarded a Nobel Prize (1946) for his discovery that X-rays cause mutations and alter phenotype.

[16] *S Luria* and *M Delbruck* (1943)

[17] *RB Goldschmidt* (1878-1958), a proponent of its dynamic features, showed genetics at work by observing the change in frequency of pigmentation in a population of moths under natural selection (1921); the evolutionary implications were obvious to him.

[18] *AH Bradshaw* (1952) shows evidence in grasses for natural selection of genotypes tolerant to high concentrations of heavy metals in soil.

[19] *OT Avery*, *CM MacLeod* and *M McCarty.* "Studies on the chemical transformation of pneumococcal types". *J Exp Med* 79:137-158 (1944). This paper "transformed" our ideas about the role of DNA.

[4] vide supra

grasses.[18] The phenomenon is still further recognized in transformation of the pneuomococcus, bringing about a change in its virulence; this will lead Oswald Avery and colleagues[19] to identify DNA as the "transforming principle". However the actual physical structure of the gene remains elusive.

Erwin Schrödinger, introduces a new reality in the concepts imbedded in his four famous lectures.[4] He proposes the existence of an aperiodic solid polymer with potential as a miniature code containing information transmitted from one generation to the next. The insight becomes a reality when a discrete chemical polymer isolated from cell nuclei is identified by Watson, Crick and colleagues[20] as the antiparallel double-helix molecule of DNA; it becomes the materialists' candidate for the "life code". Because DNA has the property of replication it can fulfill the biological paradigm of information transmittal[21]; because it is mutable it can also be the vehicle for evolution of inherited phenotypic variation.

The genetic vocabulary was soon revealed to be a redundant 3-letter code which is both transcribed and translated; Crick called it a unidirectional "central dogma" (DNA (copy) makes RNA (copy) makes protein (copy))[22]. Because protein cannot make a complementary DNA copy, Lamarckian biology is, in one stroke of insight, extinguished. And so, a journey continues: beginning in 1926 with recognition that an enzyme is a protein,

[20] The colleagues were *MHF Wilkins and RA Franklin*. The article that emerged is the cornerstone of modern biology; [*JD Watson and FHC Crick.* "Molecular structure of nucleic acids. A structure for deoxyribose nucleic acid". *Nature* 171:737-738 (April 25) 1953]

[21] The paper by Watson and Crick contains the famous paragraph: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for genetic material".

[22] See FHC Crick (1970) in main list of references.

[23] *JB Summer* (1926); an enzyme is a protein; *M. Schlesinger* (1934) on bacteriophage content; *GW Beadle and EL Tatum* (1944) relate genes to enzymes.

continuing in 1934 when it is shown that certain bacteriophages comprise just DNA and protein, and pausing in 1941 when the "one gene-one enzyme" hypothesis emerges[23], the heretofore mysterious links between *genotype* and *phenotype* begin to become manifest (Olby, 1974).

VIII. GENES, HUMAN EVOLUTION AND HUMAN BIOLOGY.

A prevalent human genetic disease, *sickle cell anemia*, is recognized to be inherited as an autosomal recessive trait.[24] The new historical relevance of sickle cell anemia rests in the fact that the variant protein, known as sickle globin, has an abnormal molecular structure.[25] When it becomes possible to sequence a protein, it is seen that the 6th amino acid residue (glutamate) in the normal human β globin chain is replaced by valine in the sickle globin molecule.[26] This will ultimately be explained by a nucleotide change (mutation) in the nuclear DNA; adenine is replaced by thymine in the sixth codon of the transcribed and translated human *HBB* gene on the short arm of chromosome 11 in banding region 15 (chromosome 11p15).

The very high prevalence (up to 18% of the gene copies) of the sickle cell mutation in some human populations along with other

[24] See *JV Neel* "The Inheritance of sickle cell anemia" *Science* 110:64-66 (1949). However, in another landmark paper in human genetics, *Garrod* had revealed much earlier that humankind observes Mendel's rules of inheritance and heredity will explain some of our personal idiosyncratic relationships with experience (see AE Garrod. *Lancet* 2:1616-1620(1902)).

[25] Another landmark observation; *L Pauling, HA Itano, SJ Singer, IC Wells*. "Sickle Cell Anemia, a Molecular Disease". *Science* 110:64-66 (1949).

[26] *VM Ingram* "A specific chemical difference between the globins of normal human and sickle-cell anemia hemoglobin" *Nature* 178:792-94 (1956).

[27] *AC Allison* (1954) proposes positive natural selection in sickle cell heterozygosity at the β globin locus; Haldane (1946) proposes it in thalassemia carriers, in both cases through *P. falciparim* malaria infection. *LH Miller* (1976) proposes a corresponding relationship for Duffy blood group by *vivax* malaria; Fy^-/Fy^- persons are resistant to *P.vivax* infection. *SA Tishkoff et al*. measure nucleotide diversity and linkage disequilibrium at the human *G6PD* locus and demonstrate evidence for human evolution under natural selection against plasmodium parasite infection, suggesting further that malaria has had a major impact on human biological

mutations causing *thalassemia*[27], and of mutations causing *G6PD enzyme deficiency* in red blood cells, is attributed to balanced selection against ubiquitous *falciparum* malaria infection in the corresponding geographic regions of the world;[27] the high prevalence of Duffy blood group in certain tropical populations is also explained by selection against *Vivax* malaria[27]. That carriers of α thalassemia-causing mutations have a selective advantage against malaria infection is revealed in a vast project[28]. *Homo sapiens* thus harbours convincing evidence that it, like all other species, experiences natural selection and spontaneous evolution of biological diversity.

Relevance of The Cell Cycle

Replication and distribution of the chromosomal DNA content through 4 phases of cell division (mitosis) in somatic cells, involves specific chromosomal behaviour[29]. Mutation affecting regulation of the *cell cycle* can lead to autonomy (and anarchy) in growth and lifespan of a cell clone; it becomes apparent that such an event can be at the heart of the cancer process.

An error in quantitative distribution of all or part of human chromosome 21 into gametes, resulting in triploid instead of diploid dosage, is recognized to be the cause of Down syndrome.[30] The process by which the distribution of chromosomes occurs, and thus of genes, during eukaryotic cell division is finally shown to be a very old one on Earth; it is

adaptation since the introduction of agriculture during the past 10,000 years (*Science* 393: 455-462, 2001).

[28] *J Flint et al*. "High frequencies of α thalassemias are the result of natural selection by malaria". *Nature* 321:744-(1986). This paper rigorously documents evidence for natural selection in action in Melanesian populations.

[29] *A Howard, SR Pelc*. (1953) describe 4 stages in the cell cycle: G1 with no DNA synthesis; S when DNA content doubles; G2 is a phase of cellular growth; M is the phase when mitosis (cell division) occurs.

[30] Misadventure in the distribution of chromosome 21, resulting in a triploid 21 genomic complement, is discovered to be the origin of the human Down syndrome. (J *LeJeune, M Gauthier, R Turpin. C. R. Acad. Sci.* (Paris) 248:1721-22 (1959))

[31] *A Knoll, ES Barghoorn* (1977) find evidence compatible with cell division in microfossils imbedded in very old rocks.

identifiable in microfossils some 3.4 billion years old in the Lower Archean era[31].

IX. ENVOIE

The links between the theories of Darwin and Wallace concerning Evolution by Natural Selection and the evidence that genes encode heredity are rich and dense. Heredity, human genes and evolution escape illusion and become realities via multiple paths of information and knowledge.

The paths penetrate five forms of knowledge, recognizable as: - the unknowable, the unknown, the known, the I-don't-want-to-know, and the forbidden. A chemical, knowable (materialistic) view of Life has intruded on a vitalistic unknowable (divine) view (Kirschner et al. 2000). While it is appropriate to know that a human or any other life is much more than the materialism of its genetics, nonetheless heredity and genes are part of Life and of being human; they do not belong in the domain of forbidden knowledge. Our ancestors evolved; the corresponding information and knowledge has evolved; the corresponding wisdom can evolve. We have the choice to participate in the their evolution.

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Bibliography

Crick FHC (1970) Central Dogma of Molecular Biology. *Nature* 227:561-563

Dawkins R (1989). *The Selfish Gene*. Oxford Univ. Press. New Edition.

Dawkins R (1995) *River out of Eden. A Darwinian View of Life.* Wiedenfeld and Nicolsen.

Dobzhansky Th (1973). Nothing in biology makes sense except in the light of evolution. *Am Biol Teacher* 35:125-129.

Eiseley L (1958) *Darwin's Century. Evolution and the Man who Discovered it*. Doubleday and Co. Inc.

Hartman JL IV, Garvik B, Hartwell L (2001). Principles for the buffering of genetic variation. *Science* 291:1001-1004.

Jacob F (1982) *The Possible. The Actual*. Univ. Washington Press.

Judson HF (1979) *The Eighth Day of Creation. Makers of the Revolution in Biology*. Simon and Schuster.

Kacser H, Burns JA (1981). The molecular basis of dominance. *Genetics*. 97:629-666.

Kirschner M, and Gerhart J (1998). Evolvability. *Proc Nat Acad* Sci 95:8420-8427.

Kirschner M, Gerhart J, Hutchison T (2000) Molecular "vitalism". *Cell* 100:79-88.

Mayr E (1982) *The Growth of Biological Thought. Diversity, Evolution and Inheritance*. The Belknap Press of Harvard Univ. Press.

Olby R. *The Path to the Double Helix*. Univ. Washington Press. 1974.

Schrödinger E. (1944) *What is Life? The Physical Aspect of the Living Cell*. Cambridge Univ. Press (Canto Edition).

Sober E (1984) *The Nature of Selection. Evolutionary Theory in Philosophical Focus*. A Bradford Book. The MIT Press.

Strohman R (2002) Maneuvering in the complex path from genotype to phenotype. *Science* 296:701-703.

Weismann A (1889). The author's paper on the duration of life is translated and included in Poulton EB, Sholand S, and Shipley AE (eds). (1993). *Essays upon Heredity and Kindred Biological Problems.* Press, Oxford. pp. 1-66.