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What prevents mainstream evolutionists teaching the whole truth about how genomes evolve?

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ABSTRACT

The common belief that the neo-Darwinian Modern Synthesis (MS) was buttressed by the discoveries of molecular biology is incorrect. On the contrary those discoveries have undermined the MS. This article discusses the many processes revealed by molecular studies and genome sequencing that contribute to evolution but nonetheless lie beyond the strict confines of the MS formulated in the 1940s. The core assumptions of the MS that molecular studies have discredited include the idea that DNA is intrinsically a faithful self-replicator, the one-way transfer of heritable information from nucleic acids to other cell molecules, the myth of "selfish DNA", and the existence of an impenetrable Weismann Barrier separating somatic and germ line cells. Processes fundamental to modern evolutionary theory include symbiogenesis, biosphere interactions between distant taxa (including viruses), horizontal DNA transfers, natural genetic engineering, organismal stress responses that activate intrinsic genome change operators, and macroevolution by genome restructuring (distinct from the gradual accumulation of local microevolutionary changes in the MS). These 21st Century concepts treat the evolving genome as a highly formatted and integrated Read–Write (RW) database rather than a Read-Only Memory (ROM) collection of independent gene units that change by random copying errors. Most of the discoverers of these macroevolutionary processes have been ignored in mainstream textbooks and popularizations of evolutionary biology, as we document in some detail. Ironically, we show that the active view of evolution that emerges from genomics and molecular biology is much closer to the 19th century ideas of both Darwin and Lamarck. The capacity of cells to activate evolutionary genome change under stress can account for some of the most negative clinical results in oncology, especially the sudden appearance of treatment-resistant and more aggressive tumors following therapies intended to eradicate all cancer cells. Knowing that extreme stress can be a trigger for punctuated macroevolutionary change suggests that less lethal therapies may result in longer survival times.

1. Introduction

It is often taken for granted that the fundamental problems of evolutionary biology were solved on the basis of random mutation and natural selection by Charles Darwin (Darwin, 1859) and his 20th Century followers who formulated the so-called "Modern Synthesis" of Darwinism and Mendelian genetics (Huxley, 1942). However, that comfortable assumption is inconsistent with a large body of research over more than a century that has documented more biologically complex processes at work in evolution. Table 1 lists some of the pioneering scientists whose discoveries and insights have proved difficult to incorporate into the basic tenets of the Modern Synthesis.

As we shall see below, all these pioneers have minimal or zero recognition in standard Evolutionary Biology textbooks. They have been uniformly sidelined for working on phenomena that lay outside the assumptions of The Modern Synthesis (MS). Although many exponents of MS may acknowledge the validity of the research and arguments of these scientists, they claim their work is compatible with the MS without ever providing detailed explanations of how that compatibility is possible.

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Table 1
Un- and under-acknowledged pioneers in evolution research.

Pioneer	Discovery/Insight	Reference
Richard Goldschmidt (1878–1958)	Macroevolution (formation of new species and taxa) is different from Microevolution	Goldschmidt (1982)
Boris Mikhailovich Kozo-Polyansky, (1890–1957)	Evolution by symbiosis, or symbiogenesis	Kozo-Polyansky (2010)
Barbara McClintock (1902–1991)	Chromosome restructuring after breakage; mobile genetic "controlling elements"	McClintock (1987)
Conrad Waddington (1905–1975)	Epigenetic control of genome function	Waddington (1957)
Roy J. Britten (1919–2012)	Repetitive DNA in the genomes of complex organisms	Britten and Kohne (1968)
Carl Woese (1928–2012)	*Archaea*, a third realm of life	Woese and Fox (1977)
Lynn Margulis (1938–2011)	Symbiogenetic origin of eukaryotic cells	Margulis (1970)
Stephen Jay Gould (1941–2002)	Punctuated equilibrium in the fossil record	Gould (1983)

2. Active vs passive views of evolution

One of the main distinctions between the MS and macroevolutionary views of speciation and taxonomic diversification lies in the role assigned to the evolving organisms.

In the MS, the organism and its descendants are passive recipients of the variation of two processes outside their control: random mutations and Natural Selection. From an evolutionary perspective, the only task of the randomly mutated organism is to reproduce more rapidly than its unmutated kindred. In particular, there is no organismal input into the process of hereditary variation, which is nowadays attributed by the MS to accidents in genome replication (Brenner, 2012).

In contrast to the MS, the macroevolutionary perspective views the evolving organism as an active participating agent in generating its own hereditary variation and modifying the selective environment. Rather than a ROM (Read only Memory) data storage system changed by accident, the genome becomes a RW (Read–Write) database for cell and organism reproduction (Shapiro, 2013, 2017). In other words, in the 21st Century view of evolution, the processes of organismal and genome change become core biological functions, and the ability to evolve actively is fundamental to the maintenance of life.

3. Macroevolution is not the same as microevolution

As we consider how cancer evolves, it is necessary to define more precisely what we mean by "evolution". Macroevolution is not the same as microevolution. Microevolution is the gradual evolution optimizing individual adaptations by accumulation of independent localized mutations, that Darwin described in 1859:

> "If it could be demonstrated that any complex organ existed, which could not possibly have been formed by numerous, successive, slight modifications, my theory would absolutely break down. But I can find out no such case" (Darwin, 1859).[1]

Macroevolution, on the other hand, is rapid punctuated evolution generating new species and new taxa that involves chromosome or karyotype restructuring (Goldschmidt, 1982; Stebbins and G.L., 1951; White, 1945; Heng, 2019). We understand a lot more about microevolution because it has dominated evolutionary studies for over a century. However, microevolutionary models for tumor progression have proved inadequate because cancer is a disease of macroevolution. We have known about macroevolution for over 80 years, since Goldschmidt devoted half of his 1940 book *The Material Basis of Evolution* to that subject. Unfortunately, Goldschmidt was virtually completely dismissed by the mainstream evolution establishment.

It is worth quoting at some length what Goldschmidt wrote 80 years ago because he reasoned so lucidly and presciently anticipated contemporary perspectives highly relevant to cancer progression (Heng, 2019):

> "We started this chapter with the conviction, gained from an unbiased analysis of all pertinent Facts, that microevolution by means of micromutation leads only to diversification within the species, and that the large step from species to species is neither demonstrated nor conceivable on the basis of accumulated micromutations. We have long been seeking a different type of evolutionary process and have now found one; namely, the change within the pattern of the chromosomes…the classical theory of the gene and its mutations did not leave room for any other method of evolution {than microevolution}. Certainly, a pattern change within the serial structure of a chromosome, unaccompanied by gene mutation or loss, could have no effect whatsoever upon the type and therefore no significance for evolution {on the classical theory}. But now pattern changes are facts of such widespread and, as it seems, typical occurrence that we must take a definite stand regarding their significance…
>
> More and more facts are accumulating which show that the intimate serial pattern of the chromosome is important for the action of the hereditary material. Chromosome breaks which lead to new serial arrangements of the parts of the chromosome; namely, deficiencies, inversions, duplications, and translocations…may produce definite genetic effects, which are not different from the typical effects of mutations. Such effects have been called "position effects", a term implying that the genes have some kind of action upon each other and that, therefore, it makes a difference whether they are located side by side or separated…

[1] In his later works, Darwin was more nuanced in his ideas. His 1868 book (Darwin, C., *The Variation of Animals and Plants under Domestication, 2 vols.* 1868, Edinburgh, John Murray) included a pangenetic theory of inheritance of acquired characteristics and his 1871 book (Darwin, C *The Descent of Man, and Selection in Relation to Sex.* 1871. Edinburgh, John Murray.) formulated his theory of sexual selection, which postulates an active role for the organisms. We should also note that Darwin modified his position in later editions of *The Origin of Species* to acknowledge "variations which seem to us in our ignorance to arise spontaneously. It appears that I formerly underrated the frequency and value of these latter forms of variation, as leading to permanent modifications of structure *independently of natural selection*" (*Origin of Species*, 6th edition, Chapter 15, p. 395, emphasis ours).

Table 2
Active cellular processes leading to taxonomic diversification and adaptations.

Process	Cell functions involved	Historical Examples	References
Symbiogenetic cell fusion	External adherence, invasion, phagocytosis, integration into host cell cycle	Origin of the eukaryotic cell and photosynthetic eukaryotes	Archibald (2014), Margulis (1981) and Martin et al. (2015)
Infectious heredity	Intercellular DNA transfer by viruses, plasmid-mediated conjugation	Bacterial antibiotic resistance, toxin production, root symbiosis	Cavalli et al. (1953), Zinder and Lederberg (1952), Lederberg (2000) and Roberts (2014)
Horizontal DNA transfer across taxa	Viral, bacterial or parasite infection, arthropod predation, foreign DNA integration	Invertebrate phyto-polymer digestion, symbiotic nitrogen fixation, bacterial virulence	Haegeman et al. (2011), Weber and Faris (2018), Best and Abu Kwaik (2018) and Wybouw et al. (2016)
Natural Genetic Engineering	Mutagenic polymerases, nucleases, ligases, recombinases, transposases, reverse transcriptases, mobile genetic elements	Antibiotic resistance, exon shuffling, pseudogenes, viviparous reproduction	Shapiro (2011), Jiang et al. (2004), Lynch et al. (2015), Chuong (2018) and Vinckenbosch et al. (2006)
Holobiont symbiosis	Infection and establishment in host tissues and organs	Metabolism, immune response, mental state	Kundu et al. (2017), Salvucci (2014) and Hoban et al. (2017)
Hybrid speciation (“Cataclysmic Evolution”)	Epigenetic deregulation of mobile DNA, chromosome rearrangement, whole genome doubling	Wine yeasts, large majority of crop plants, Galapagos finches	Stebbins and G.L. (1951), Abbott et al. (2013), da Silva et al. (2015), Chester et al. (2012) and Lamichhaney et al. (2017)
Responses to ecological changes	Activation of NGE functions, genome rearrangements	All organisms	Shapiro (2017) and online references cited there[a]
Niche Construction	Modification of the external environment	Yeast, diatoms, earthworms, ants and termites, birds, human beings	Darwin (1890), Odling Smee et al. (2003), Erwin (2008) and Buser et al. (2014)

[a] https://shapiro.bsd.uchicago.edu/Ecological_Factors_that_Induce_Mutagenic_DNA_Repair_or_Modulate_NGE_Responses.html.

> A repatterning of a chromosome may have exactly the same effects as an accumulation of mutations. And even more, a complete repatterning might produce a new chemical system which as such; i.e., as a unit, has a definite and completely divergent action upon development, an action which can be conceived of as surpassing the combined actions of numerous individual changes by establishing a completely new chemical system. Model: two different pictures produced with the same set of mosaic blocks, the new picture “emerging” only when all blocks are in their proper place. It is certainly most remarkable that the new developments in genetics lead to the same conclusions which are derived as postulates from an unbiased analysis of the evolutionary facts. This encourages me to believe that the dead end reached by the neo-Darwinian theory based upon the assumptions of classical genetics can now be passed successfully” (Goldschmidt, 1982). {Brackets added}

It is important to note that the two modes of evolution operate differently over time. Microevolution operates gradually and more or less continuously depending upon the observed mutation rate. Macroevolution, on the other hand, occurs in a punctuated manner, depending upon episodic stress-induced processes which lead to chromosome restructuring (Shapiro, this issue).

4. Not all hereditary variation is vertically transmitted or limited to the germline

Another basic assumption of the MS is that all change to genomes occurs internally and is transmitted vertically strictly within a line of descent. When a taxonomic divergence occurs in this view, it represents a branch on the “tree of life”, as diagrammed by Darwin at the end of *Origin of Species* (Darwin, 1859), and by Lamarck at the end of his 1808 *Zoologie Philosophique* (Lamarck, 1994; Hellström, 2012; Voss, 1952). Since the middle of the 20th Century, we have learned of numerous cases where *horizontal* transfers of genome information have contributed in important ways to evolutionary change. Molecular evolutionists have argued that is therefore more appropriate to speak of a “web of life”, where the genomes of different taxa interact, than it is to think only of an ever-branching tree (Sinkovics, 2011; Soucy et al., 2015; Daubin and Szollosi, 2016; Shapiro, 2019).

Some examples of horizontal transfer of pre-evolved genetic information include the following:

- The most impactful example of the evolutionary potential of inter-taxa genome transfers came to light in the 1960s as a consequence of mankind’s largest-scale evolution experiment, the global application of antibiotics in medicine and agriculture. Although bacteria were expected to evolve resistance by internal genome mutations, according to conventional (and experimentally confirmed!) MS ideas, in the real world of the clinics and farms, the vast majority of bacteria acquired drug resistance in the form of transmissible antibiotic resistance (R-factor) plasmids (Watanabe, 1967; Bukhari et al., 1977). Many of these R-factors evolved by NGE processes (transposition and site-specific recombination) to carry multiple resistance determinants and provide virtually instantaneous adaptations to a range of antibiotics in the arms race between human attempts to eradicate and bacterial attempts to survive (which the bacteria are currently winning) (CDC, 2019; Stalder et al., 2012; Lerminiaux and Cameron, 2019).
- A different form of virtually instantaneous infectious heredity in bacteria involves the acquisition of adaptive traits by viral infection. These traits can involve host cell DNA packaged into viral particles instead of viral DNA (generalized transduction) or viral DNA that integrates into the host genome along with the rest of the viral genome (specialized transduction) (Fillol-Salom et al., 2019; Waddell et al., 2009; Morse et al., 1956; Coetzee, 1975). Viruses likewise serve as horizontal DNA vectors in eukaryotes (Wang and

Wu, 2017). Specialized transduction has been important in the evolution of bacterial pathogens because most of them acquired the ability to produce toxins by integrating viral genomes that encode them, in a process labeled "lysogenic conversion" (Brussow et al., 2004; Kraushaar et al., 2017; Askora et al., 2017). Microbiologists attribute the adaptive significance of many bacterial toxins less to pathogenicity in animals and more to protection against microbial eukaryotic predators in the bacteria's natural environment (Silveira and Rohwer, 2016).

• In addition to active virus infections, horizontal DNA transfers across wide taxonomic barriers, such as bacteria to plants and animals or the reverse, can occur by an unexpectedly broad variety of methods (https://shapiro.bsd.uchicago.edu/Modes_of_Horizontal_DNA_Transfer.html):

(i) encapsidation and transfer by "virus-like particles" (VLPs) and "gene transfer agents" (GTAs) produced by cells in the absence of viral infection;
(ii) incorporation into extracellular vesicles (EVs) that are produced by all types of living cells (Yanez-Mo et al., 2015; Kawamura et al., 2019; Fischer et al., 2016; Tran and Boedicker, 2017);
(iii) uptake of naked DNA from the environment, including DNA liberated from viral vectors (Keen et al., 2017);
(iv) direct cell–cell contact ("conjugation"), cell fusion, and phagocytosis;
(v) parasite, pathogen or endosymbiont infection;
(vi) arthropod predation (Di Lelio et al., 2019)

Since many bacteria and viruses can infect more than one host, such as humans and amoebae, they are potential vectors for multi-step DNA transfers across large taxonomic divides (Husnik and McCutcheon, 2018; Gilbert and Cordaux, 2017). Of particular interest in this regard are the "giant viruses" (*Megaviridae*) whose large genomes (500 Kb to >2.5 Mb) have been dubbed "genomic accordions" because the mosaic viral DNAs expand and contract by accumulating and deleting non-viral sequences, including those from all three domains of life (Colson et al., 2013; Filée, 2009; Filee, 2013; Colson et al., 2018).

These megaviruses coexist in amoeba (hosts described as "evolutionary melting pots") together with bacteria that also infect humans and other animals (*Rickettsia*, *Legionella*, etc.) (Wang and Wu, 2017; Moliner et al., 2010; Boyer et al., 2009; Wilhelm et al., 2017). Bacteria- and amoeba-megavirus DNA exchanges have been documented (Filee et al., 2007; Bertelli and Greub, 2012; Maumus and Blanc, 2016; Koonin and Yutin, 2018), and they can then be precursors to further horizontal transmissions upon escape of either the virus or the bacteria to infect other eukaryotic hosts.

5. The end of "selfish" or "junk" DNA

A major shortcoming of the MS is that it was based on a "gene-centric" view, which assumed that the genome is basically a collection of "genes" that are the protein-coding units of heredity and heritable variation. As we saw in the quotation from Goldschmidt's 1940 book, this view failed to take the evolutionary importance of chromosome structure into account (Goldschmidt, 1982). It also blinded evolutionary biologists to the importance of McClintock's mid-20th Century discovery of mobile "controlling elements" (McClintock, 1987). Both the ideas of genetic transposition and control of gene expression by these non-coding mobile elements did not fit within the narrow confines of the MS concepts of genome function and variation. A further empirical assault on the limited MS conceptual framework came in the late 1960s when Britten and Kohne discovered that a significant fraction of genomic DNA from complex eukaryotes consists of highly repetitive sequences rather than the unique coding sequences expected to make up the hereditary material (Britten and Kohne, 1968).

In order to apply selectionist thinking to explain the presence of so much non-coding DNA, evolutionary biologists called this unexpected portion of the genome "junk DNA" (Ohno, 1972) or "selfish DNA" (Orgel and Crick, 1980). Richard Dawkins used an extreme view of these "selfish genes" to erect a whole philosophy of strictly passive evolutionary gradualism (Dawkins, 1976). Today we know that the human genome contains at least 30X as much repetitive non-coding DNA as protein-coding sequences (Lander et al., 2001). Repetitive DNA provides formatting signals for transcription, epigenetic modification and chromosome mechanics and also is the most variable component in the evolutionary diversification of complex genomes (Symonová and Howell, 2018; Subirana et al., 2015; Matsubara et al., 2016; Cioffi Mde et al., 2015; Chalopin et al., 2015; Shao et al., 2019; Böhne et al., 2008; Li et al., 2016; Oliver et al., 2013). A 2013 plot of organismal complexity against protein-coding and non-coding DNA showed that coding DNA peaked at approximately $\sim 3 \times 10^7$ bp, while the non-coding DNA increased linearly with growing complexity up to $\sim 2–3 \times 10^{10}$ bp (Liu et al., 2013). In other words, non-coding DNA tracked organismal complexity better than the protein-coding genes. The "encyclopedia of DNA elements" (ENCODE) project, which largely abandoned the term "gene", revealed that the large majority of the so-called junk DNA is actively transcribed in a regulated manner, indicating that it is functional (Consortium, 2012; Pennisi, 2012).

Our current understanding of mobile and repetitive DNA element functionality falls into two categories relevant to evolutionary change. The first category follows McClintock and also Britten and Davidson in recognizing that this fraction of the genome can format transcriptional and epigenetic regulatory networks (Britten and Davidson, 1971; Britten, 1996; Shapiro and Sternberg, 2005). Among the evolutionary innovations wired by these mobile repeats are C4 photosynthesis in plants and viviparous reproduction in mammals (Lynch et al., 2015; Chuong, 2018; Cao et al., 2016; Chuong et al., 2017). The second category of functional significance for repetitive DNA elements is that they make up a large fraction of the DNA transcribed into non-coding ncRNAs that are key to cellular differentiation, genome expression (*e.g.*, forming long-distance transcription complexes), epigenetic regulation (siRNAs) and coordination of all kinds of phenotypes, such as fruit ripening in tomatoes, sex determination in *Drosophila*, and pluripotency in human stem cells (https://shapiro.bsd.uchicago.edu/Regulatory_Functions_Reported_for_Long_Non-%20coding_lncRNA_molecules.html). Clearly, none of the eminent scientists who wrote about junk or selfish DNA could possibly have imagined the wide range of cellular functionalities that we know today are executed by ncRNA molecules. The idea that a genome was just a collection of protein coding sequences has proved completely inadequate.

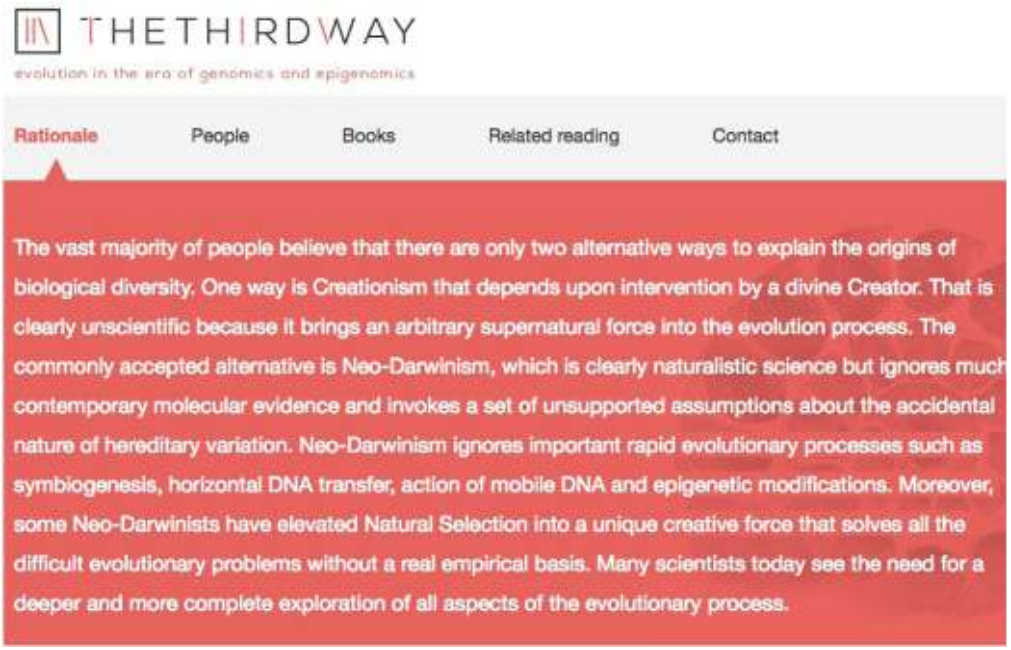

Fig. 1. Screenshot of mission statement from http://www.thethirdwayofevolution.com/.

6. The third way of evolution

In order to make it clear that the MS is far from the last word on "descent with modification", in 2013 the two of us and Raju Pookottil founded the group named "the Third Way of Evolution" (http://www.thethirdwayofevolution.com/). Our aim was to create a space in which dissenters from the Modern Synthesis can work and develop insights. The THIRDWAY rejects Creationism as unscientific and the Modern Synthesis as too restrictive and unable to incorporate discoveries in genomics. The group is independent of any particular "synthesis" because there are still many unpredictable discoveries to be made about evolutionary processes.[2] The THIRDWAY seeks to validate and open new research lines in evolutionary biology, as stated in its online mission statement below (Fig. 1).

One way of documenting the difference in approaches between conventional evolutionary science and THIRDWAY members is to compare current publications and how often they cite the results of genomic analysis that have broadened the evolutionary perspective (Table 3).

Table 3 lists the key publications relevant to the Modern Synthesis, listing first the foundations leading to the Synthesis, and then the developments outside the Synthesis. The columns show (left) the dates of publication, (middle) the authors, (right) the discoveries and their references.

The results of our analysis of references to discoveries are shown in the middle column of Table 3 as total numbers of citations in five leading neo-Darwinist texts: *Evolution* (Futuyma and Kirkpatrick, 2018), *Why Evolution is True* (Coyne, 2010), *The Selfish Gene* (Dawkins, 1976), *The Extended Phenotype* (Dawkins, 1982), and *The Blind Watchmaker* (Dawkins, 1986). A standard character indicates a zero which does not signify a negative attitude to the work or people concerned. **Bold** indicates positive references to those names. *Italics* indicates neglect (zero score) or a derogatory reference. Red numbers indicate references in Futuyma & Fitzpatrick, *Evolution* (2018) (Futuyma and Kirkpatrick, 2018). Blue numbers indicate references in Coyne, *Why Evolution is True* (2010) (Coyne, 2010). Green indicates references in Dawkins in the order: *The Selfish Gene* (1976) (Dawkins, 1976) , *The Extended Phenotype* (1982) (Dawkins, 1982)), *The Blind Watchmaker* (1986) (Dawkins, 1986). For developments outside the Modern Synthesis, data has been added from the 3 Dawkins books in a single total.

The relative absence of references to T.H. Morgan in Table 3 is strange. Many of his ideas are foundational to the Modern Synthesis. This item in the table should be in **bold** font. Morgan was the discoverer of the role that the chromosomes play as carriers of genes in heredity, for which he received a Nobel Prize in 1933. Apparently, his work was just taken for granted in the publications we analyzed. The data on Lynn Margulis are important, and we will return to the subject of Symbiogenesis below. Similarly, the neglect of Goldschmidt's ideas about macroevolution has already been discussed. The neglect of C.H. Waddington is also not a surprise. He was deliberately excluded from the group that first developed the MS because of his ideas outside the contemporary mainstream (Peterson, 2011). Dawkins has one reference to Waddington on page 44 in *The Extended Phenotype* (1982) (Dawkins, 1982), where his work is conflated with the Baldwin Effect, a misunderstanding of what Waddington actually asserted (see Noble, 2016, pp 216–219). Some of Lederberg's ground-breaking work on bacteria is referenced, but note that horizontal transfer of DNA is not mentioned. Temin's similarly ground-breaking work on reverse transcription received little attention. In *The Extended Phenotype*, Dawkins introduces Temin in the context of discussing Steele's work. Temin is just a side story, but at least he doesn't challenge the Temin work or the mechanism of reverse transcription of RNA to DNA. Doolittle is referenced in *The Extended Phenotype*, but, surprisingly, not on the origin of

[2] For example, it is less than 50 years since Woese and colleagues unexpectedly discovered *Archaea* in 1977, which ultimately made it possible to document the symbiogenetic origin of eukaryotes as a fusion of a Proteobacterium and an Asgard archaeon about 2 GYA (Spang, A., et al. Asgard archaea are the closest prokaryotic relatives of eukaryotes. *PLoS Genet*, 2018. **14**(3): p. e1007080).

Table 3
Key publications relating to evolution biology.

Foundations leading to modern synthesis		
Dates	People	Discovery/Field/Topic/Reference
1859	Charles Darwin **37 57 7 6 12**	Natural Selection (Darwin, 1859)
1893	August Weismann **1 0 1 5 0**	Weismann Barrier (Weismann, 1893)
1915	T H Morgan 0 0 0 0 **1**	Chromosomal basis of Mendelian Genetics (Morgan et al., 1915)
1930	Ronald Fisher **6** 0 **6 12 6**	Population statistics (Fisher, 1930)
1932	Sewell Wright **4** 0 0 **9** 0	Adaptive landscape (Wright, 1932)
1932	J B S Haldane **5 1 2 3 1**	Population Genetics (Haldane, 1932)
1941	Beadle & Tatum 0 0 0 0 0	One Gene – one protein correlation (Beadle and Tatum, 1941)
1942	Julian Huxley **1** 0 0 **3 3**	Modern Synthesis (Huxley, 1942)
1953	Franklin & Gosling 0 0 0 0 0 Watson & Crick **1** 0 0 0 **5**	DNA double helix (Franklin and Gosling, 1953; Watson and Crick, 1953a)
Developments outside modern synthesis		
Dates	People	Discovery/Field/Topic + Reference(s)
1910 1924 1971	Mereschkowsky *0 0 0* Kozo-Polyansky *0 0 0* Lynn Margulis 1 *0* **6**	Macroevolution by symbiogenesis (Mereschkowsky, 1910; Kozo-Polyansky, 1924; Margulis, 1971)
1940 2019	Goldschmidt *3 1 1* Heng *0 0 0*	Distinction between Darwinian microevolution and non-Darwinian macroevolution (Goldschmidt, 1982; Heng, 2019)
1950–1953	Barbara McClintock *0 0 0*	Transposable elements (McClintock, 1987)
1942–1957	Conrad Waddington *1 0 1*	Transgenerational inheritance of acquired traits (Waddington, 1957, 1977)
1952	Lederberg et al 1 0 0	Infective heredity and horizontal DNA transfer in bacteria (Lederberg et al., 1952)
1953 1966 1998	Weigle *0 0 0* Witkin *0 0 0* Goodman *0 0 0*	Cell-induced mutability (Weigle, 1953) Error-prone SOS DNA repair (Witkin, 1966) Mutator polymerases (Goodman, 1998)
1970	Temin *0 0* 1	Reverse transcription of RNA into cDNA (Temin and Mizutani, 1970)
1968	Britten *0 (but see next) 0 0*	Repetitive DNA content of complex genomes (Britten and Kohne, 1968)
1971	Britten & Davidson **1** *0 0*	Repetitive DNA elements formatting regulatory networks (Britten and Davidson, 1971)
1972 1975 1975	Pigott & Carr *0 0 0* Bonen & Doolittle *0 0 0* Zablen, Kissel et al *0 0 0*	Chloroplasts originating from cyanobacterial endosymbionts (Pigott and Carr, 1972; Bonen and Doolittle, 1975; Zablen et al., 1975)
1977	Maxam & Gilbert *0 0 0* Sanger, Air et al *0 0 0*	DNA sequencing (Sanger et al., 1977; Maxam and Gilbert, 1977)
1977	Bukhari, Shapiro & Adhya *0 0 0*	Broad taxonomic and mechanistic diversity of mobile genetic elements (Bukhari et al., 1977)
1977	Woese & Fox *0 0 0*	Existence of second prokaryote kingdom (Woese and Fox, 1977)
1992 1993 1995	Ting, Rosenberg et al *0 0 0* Boyd, Bax et al *0 0 0* Venables, Brookes et al *0 0 0*	Endogenous retroviruses as transcriptional signals and contributors to placental evolution (Ting et al., 1992; Boyd et al., 1993; Venables et al., 1995)
1998 2002 2008	Fire, Xu, et al *0 0 0* Okazaki, Furuno et al *0 0 0* Dinger, Amaral et al *0 0 0*	Genome regulation by noncoding RNA (Fire et al., 1998; Okazaki et al., 2002; Dinger et al., 2008)
1998	Nevo *0 0 0*	Ecological Activation of NGE activities (Nevo, 1998)
1997	Torkelson, Harris et al *0 0 0*	Hypermutable States in Non-growing Bacteria (Torkelson et al., 1997)
2001	Lander, Linton et al *0 0 0*	Sequencing of the human genome (Lander et al., 2001)
2000 2005 2006	Giordano et al *0 0 0* Smith & Spadafora *0 0 0* Pittoggi et al *0 0 0*	Reverse transcriptase in mouse sperm (Giordano et al., 2000) Sperm-mediated gene transfer (Smith and Spadafora, 2005) Sperm-mediated soma to germline retrogene transmission across Weismann Barrier (Pittoggi et al., 2006)
2013	Guerrero, Margulis et al *0 0 0*	Microbiomes and holobiont evolution by symbiont gain and loss (Guerrero et al., 2013)

chloroplasts. Regarding the neglect of the centrally important discovery of mobile genetic elements, we checked 22 separate reference lists in Futuyma and Kirkpatrick's *Evolution* (2018) (Futuyma and Kirkpatrick, 2018), but the existence of mobile genetic elements and their roles in genome modification are not addressed. In all five books examined, there is likewise no reference to the significance of mobile genetic elements as the most abundant forms of DNA in the 2001 *Nature* article on the first complete sequencing of the human genome (Lander et al., 2001). Yet, this discovery is central to understanding how complex organisms under stress reorganized their genomes during evolution.

The same citation analysis is represented graphically in Fig. 2. Table 3 and Fig. 2 show that out of at least 40 discoveries and wider developments that go beyond the framework of The Modern Synthesis, only two are cited by Richard Dawkins in his three books on evolutionary theory, two by Futuyma in his widely used undergraduate textbook *Evolution* (Futuyma and Kirkpatrick, 2018) and none by Coyne's very popular 2010 book *Why Evolution is True* (Coyne, 2010). In contrast, books by THIRDWAY authors have referred to at least 37 of the 40 innovative developments in molecular evolution (Fig. 2).

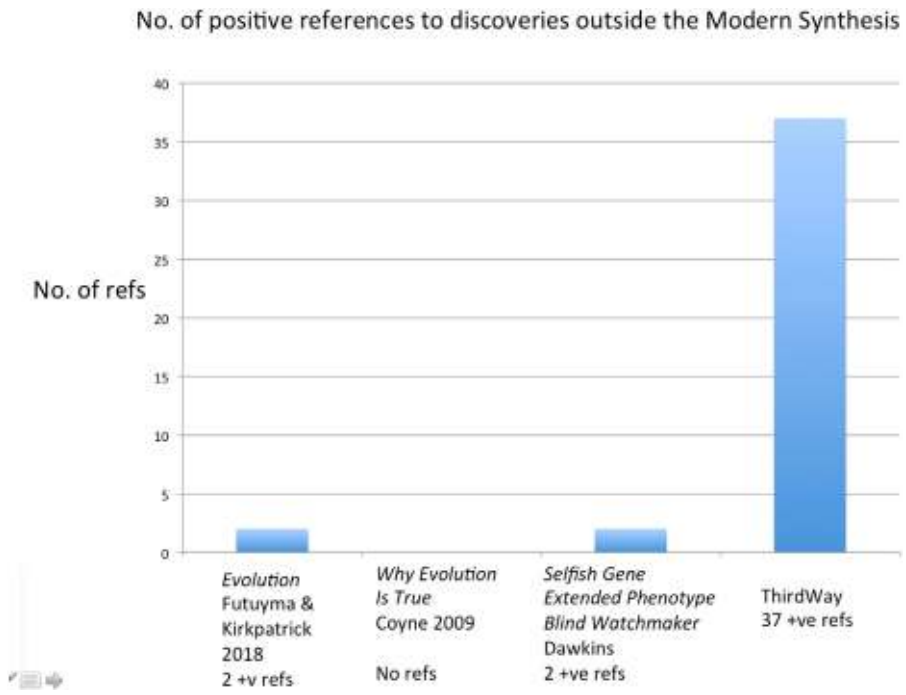

Fig. 2. Positive references to discoveries outside Modern Synthesis.

The results of this analysis are, to say the least, surprising. In which other field of biology would we find so little attention paid to so many important discoveries? The Modern Synthesis is now approaching its eightieth anniversary. Over that period almost every other aspect of biological science has undergone radical revision. The core teachings of textbooks have changed radically, and so have the popularizations. The achievements of molecular biology have shown in great detail what could not even have been imagined in 1942. A possible explanation for the lack of attention to those innovative developments is that they were perceived to require interpretation within the standard theory. Once MS proponents believed they had accomplished that reconciliation to their own satisfaction, they did not find it necessary to include or explain them in textbooks and popularizations. In the next section of this article we will therefore show why those molecular biology discoveries are actually *incompatible* with the Modern Synthesis. It is actually the Modern Synthesis that is out-of-step with Contemporary (molecular) biology.

7. Incompatibilities between the modern synthesis and molecular biology

Far from being vindicated by the discoveries of molecular biology, The Modern Synthesis is incompatible with the discoveries of molecular biology. In summing up we will highlight the central assumptions that illustrate that incompatibility.

7.1. The Central Dogma of Molecular Biology

The "Central Dogma of Molecular Biology" states that hereditary information transfers unidirectionally from genomic DNA to the proteins which are the basis for cellular and organismal phenotypes. It is based on an important discovery about the triplet code, a form of templating between nucleotide sequences and amino acid selection in protein formation (Crick, 1958). Despite its careful reformulation by Crick in 1970 after reverse transcription had been discovered (Crick, 1970), the Central Dogma says nothing about transcriptional and epigenetic regulation, insertional mutagenesis by mobile DNA elements, functional roles for non-protein coding DNA and its transcripts, or genome reorganization by organisms under environmental stress (Tables 1 and 2). Moreover, evidence from genome sequencing tells us that whole functional domains of protein coding sequences have been translocated to new genomic loci during evolution (domain shuffling) (Lander et al., 2001). There is no way in which the evolution of the proteins that acquired new domains could have been brought about by accumulation of small mutations altering the polypeptide chain one amino acid at a time. Since the process of genome reorganization is sensitive to stress on organisms, the process gives some directionality to evolution. Evolution occurs much faster by domain shuffling than by single amino acid substitutions. This is also a point of major relevance to cancer research (*e.g.,* fusion oncogenes (Imielinski and Ladanyi, 2018)), as other articles in this Special Issue show.

7.2. Accurate DNA replication

The founders of The Modern Synthesis were misled by Schrödinger's highly influential book, *What is Life?* in which he specifically used the analogy of a crystal to describe the genetic material later found to be DNA (Schrödinger, 1944). This influence was openly acknowledged by Watson and Crick (1953b). It led not only to the Central Dogma but also to the frequent popularization that "DNA molecules are astonishingly faithful (as replicators)" (Dawkins, 1976, p. 18). They are, but *not* because of growing like a crystal. Statements on DNA like "This is how crystals are formed" (Dawkins, 1976, p. 17) are simply incorrect. DNA does not form a self-replicating crystal in living organisms. Sequences longer than a few thousand bases are extremely *poor* replicators. Long DNA sequences

depend on very elaborate cellular proof-reading processes removing hundreds of thousands of copy errors in a 3 billion bp long genome to achieve faithful transmission to future generations (Perrino and Loeb, 1989; Fazlieva et al., 2009). Moreover, those error-correcting processes operate at rates and locations under control of the organism. More details can be found in three other articles by one of us in this journal (Noble, 2020a,b) (Noble, this issue).

7.3. Symbiogenesis

Arguably the most significant transition in DNA-documented evolutionary history was a symbiogenetic cell fusion between a *Proteobacterium* and an *Asgard Archaeaon* to form a unique eukaryotic ancestor (Zaremba-Niedzwiedzka et al., 2017; Spang et al., 2018). The proteobacterial endosymbiont was aerobic and ancestral to the mitochondrion and that organelle's descendants. The proteobacterial contribution enabled eukaryotes to harness energy more efficiently and eventually led to the evolution of macroscopic multicellular forms of life. The key scientist who brought this decidedly non-Darwinian transition to notice in the closing decades of the. 20th Century was Lynn Margulis (Margulis, 1970). Yet, with one exception (Richard Dawkins — see below) she is almost completely sidelined in the textbooks and popularizations we consulted. In Futuyma and Kirkpatrick's *Evolution* (Futuyma and Kirkpatrick, 2018) symbio*genesis* is not referred to at all in the section dealing with co-evolution (pp. 322–324). Margulis' work (and that of her Russian predecessors, Table 1) are not referenced in that section. The origin of mitochondria and plastids as symbionts is briefly referred to in the section on Precambrian life (p. 439). However, Margulis is not mentioned there by name. She is not in the general index either, although there is one citation to her in chapter 17 (Margulis, 1993) together with citations to later authors (Maynard Smith and Szathmáry, 1995; Moran, 2007). Symbio*genesis* as a form of *taxonomic origination* is not explicitly acknowledged. Instead the process is conflated with endosymbiosis, "which has evolved many times in the history of life". This significantly downplays Margulis' articulation of how symbiosis can lead to symbiogenesis. On that point, the textbook's citation is to Moran's paper on symbiosis (Moran, 2007) instead of Margulis's many publications on symbiogenesis. The same is true of Table 17.2 (page 437) on the major transitions in evolution, where it would have been natural to acknowledge Margulis. The Russians, Mereschkowsky (1910) and Kozo-Polyansky (1924) are not cited at all, A student could be forgiven for thinking that her work was not important enough to be openly acknowledged. Coyne's *Why Evolution is True* (Coyne, 2010) has just one brief reference to the eukaryote transition (p. 28) with no reference to symbiogenesis or to Margulis and no citations of the literature. Sexism may have played a role, but this kind of historical misrepresentation probably comes from the fact that Margulis was not a member of the Modern Synthesis "club" and was, in fact, often its critic.

The major exception among Modern Synthesis advocates is Dawkins' *The Blind Watchmaker* (Dawkins, 1986), which fully acknowledges Margulis as having shown that "mitochondria and chloroplasts, and possibly a few other structures inside eukaryotic cells, are each descended from Bacteria" (p 176). We have documented this case in more detail given the immense importance of the transitions from prokaryotes to eukaryotes and subsequently to photosynthetic eukaryotes of all kinds (Embley and Martin, 2006). Unfortunately, minimizing the importance of symbiogenesis is only too typical of what we found in relation to many of the other major discoveries that are downplayed or ignored.

7.4. The Weismann barrier and the supposed isolation of the germline genome

The idea of an impermeable barrier between the soma and the germ cells is a central feature of the Modern Synthesis. As Weismann himself emphasized, such a barrier makes the inheritance of acquired characteristics via the germ-line impossible because it would prevent information about changes in the soma influencing the germ cells (Weismann, 1893). This idea led to the common popularization that genes are "sealed off from the outside world" (p. 21. of Dawkins, 1976). The idea is falsified directly by the fact that RNAs and DNAs from the soma can be transferred to the germ cells (Pittoggi et al., 2006; Eaton et al., 2015). Moreover, in unicellular eukaryotes and in plants, the germline descends from a somatic lineage. Many forms of inheritance of acquired characteristics have now been documented. It remains for future work to determine which of these may depend on the communication of regulatory states from soma cells to the germ line.

The extent to which contrary discoveries are ignored or downplayed is well illustrated in Futuyma and Kirkpatrick's latest edition (2018) of their popular textbook, *Evolution* (Futuyma and Kirkpatrick, 2018). Their table (p. 18) listing fourteen "Fundamental Principles of Biological Evolution" qualifies five of the principles with small asterisks. These are explained as indicating that the principles have to be "qualified to some degree, in light of later research". Yet, these asterisks are placed against principles as fundamental to The Modern Synthesis as

– "Acquired characteristics are not inherited",
– "Hereditary variations are based on particles – the genes",
– "The differences between species evolve by rather small steps",
– "Species are groups of interbreeding or potentially interbreeding individuals that do not exchange genes with other such groups", and
– "Speciation usually occurs by the genetic differentiation of geographically isolated populations".

If these central principles need qualifying, then there is something wrong. They are precisely conceptual foundations the Modern Synthesis laid down 80 years ago. Yet, no explanations of the qualifications are given on that page, nor are there any links to where readers may find explanations in the 600-page book. On the contrary, as we have shown, many of the key contributors to evidence that is far more compelling than requiring "qualified to some degree" are ignored or side-lined.

Futuyma and Kirkpatrick state one key principle without giving it an asterisk:

– "Genetic variation arises by random mutation. Mutations do not arise in response to need".

Yet, despite this assertion, stresses of many different kinds (radiation, starvation, virus infection, bacterial toxins, antibiotics and DNA-damaging chemicals) have long been unambiguously documented as inducing mutagenic genome-altering processes in a wide variety of organisms. That potential has been apparent since Muller's first report of X-ray mutagenesis in 1927 (Muller, 1927), and the recognition of UV radiation's ability to induce cellular activities capable of mutagenizing *unirradiated* DNA dates back 68 years to Weigle's experiments with bacteriophages in 1953 (Weigle, 1953).

At the 2016 New Trends meeting at The Royal Society the packed audience was repeatedly told that any New Trends had already been incorporated into standard evolutionary biology textbooks. So, when were the asterisks added to this particular, and very widely used, textbook? To answer that question, we consulted the 2013 edition of Futuyma' textbook (edited by him alone). The fourteen principles are stated on pages 11–12. There are no asterisks identifying which need qualification, just the general statement "Qualifications to some of these statements are discussed in the chapters cited". Item 2 refers the reader to chapter 9, where Eva Jablonka's work is cited. But that reference is absent in the 2018 edition. Item 12 links to chapter 17 but that chapter focuses on the barriers to gene flow, while the relevant material on horizontal gene transfer is in chapter 20, where it is admitted that there has been "extensive horizontal transfer of transposons between diverse vertebrates, including primates, bats and marsupials". There is also discussion of horizontal gene transfer on pages 42–43, where it is acknowledged that "Such events violate our assumption that lineages have a strict history of separation and divergence". The other items listed above are not linked to a specific chapter. It is difficult to avoid the obvious conclusion that the revision of 2018 may have been in response to discussion at the 2016 New Trends meeting. It is also difficult to avoid the conclusion that the exceptions to the principles are downplayed and not linked to where they could be readily accessed from *the place in the text where* the principles are fully listed.

8. Misrepresentations of Darwin's theories of evolution

Finally, advocates of the Modern Synthesis misrepresent the range of Darwin's theories of evolution by narrowing them down to just two of his contributions: gradual variation and natural selection. By his own admission, Darwin was a slow and careful thinker (p. 339 of Darwin et al., 1991), and he added many significant nuances of his theories in later work. *The Origin of Species* itself developed substantially over its many editions following the first in 1859 (Darwin, 1859). By the fourth edition in 1866 he acknowledged the work of many predecessors, notably including praise for Lamarck as having upheld "the doctrine that all species, including man, are descended from other species". This praise is not surprising. Even in the first Edition of *Origin of Species*, Darwin had included the inheritance of acquired characteristics (Darwin, 1859). By 1868 when he formulated his theory of gemmules (Darwin, 1868) he was developing a mechanism for how soma characteristics could be transmitted to the germline, which resembles very closely modern work on such transmission via extracellular vesicles (Noble, 2019) (see also article by Bonner & Willms in this Special Issue). In 1871, he was elaborating his theory of sexual selection as an active, conscious activity of many organisms (Darwin, 1871). By the sixth edition of *The Origin of Species* in 1872 Darwin discussed "sports" that appeared sporadically in plants and admitted on p. 395 that he had "underrated the frequency and value of these latter forms of variation, as leading to permanent modifications of structure *independently of natural selection*" (emphasis added) (Darwin, 1872).

Although Darwin seems not to have been aware of the fact, Lamarck actually preceded him by 28 years in drawing a tree of life (Lamarck, 1809, reprinted in Noble, 2020c). Yet, one of the most popular textbooks used by students (p 13) still maintains that "Darwin's conception of the course of evolution is profoundly different from Lamarck's in which the concept of common ancestry plays no part" (Futuyma and Kirkpatrick, 2018). Like the earlier statement about DNA replicating "like a crystal", this too is incorrect.

The THIRDWAY group of scientists have a much better claim to be inheriting the mantle of Charles Darwin, and of Lamarck, than do the originators of the Modern Synthesists. For that reason, we recommend readers to consult the THETHIRDWAYOFEVOLUTION website for links to nearly 100 books that contain the details of evolutionary thinking beyond the Modern Synthesis, which we have attempted to summarize in this article.

9. Conclusions

Molecular biology and genome sequencing have given us a new way of documenting hereditary change throughout the long history of organic evolution. The genomics-based data clearly reveal a wide range of cellular and biochemical processes for creating hereditary variation and originating adaptive innovations that were largely unknown at the time the Modern Synthesis was formulated. With the exception of symbiogenesis, which was recognized by a small number of early 20th Century visionaries (Table 1), the kinds of complex genome change operations we recognize today in both organic evolution and cancer progression were literally inconceivable to the authors of the MS (Table 3). Nonetheless, the. empirical evidence for these unanticipated modes of rapid punctuated macroevolutionary change is clearly present in the growing body of genomic DNA sequences and confirmatory laboratory experiments (Shapiro, this issue).

Solid documentation in the molecular biology, genomics and oncology literatures support the ongoing revolution in thinking about macroevolutionary transformations. This rapidly growing body of empirical data makes it all the more regrettable that mainstream evolutionists still try to put the genie back in the bottle and pretend that these molecular revelations do not change the basic assumptions they propagate to students and to the general public. This campaign to convince people that nothing fundamental has changed in our understanding of evolution has been waged both in popularizations, like the books by Dawkins (1976, 1982, 1986) and Coyne (2010), and in textbooks like that of Futuyma and Kirkpatrick (2018).

The campaign to sustain the Modern Synthesis causes real harm in a number of different ways. Among doctors treating bacterial infections, ignorance of real-world evolutionary processes has led to a situation in which the available antibiotics have lost their effectiveness against many life-threatening conditions (CDC, 2019). Among the general public, the inability to comprehend the potential all living organisms possess for transferring and reorganizing genomic configurations makes them unprepared to form sound judgements about how society should utilize its growing arsenal of biotechnology tools acquired from our microbial neighbors, like CRISPR (Doudna, 2020). Among oncologists, MS thinking prevents the practitioners treating cancer patients from recognizing the dangers of overtreating tolerable tumors in ways that may provoke a macroevolutionary transition to a far more lethal and untreatable disease (Heng, 2019). Finally, in the battle against obscurantism and anti-evolution prejudice, insistence on an outdated set of assertions about how life can change itself leaves the defenders of rigorous scientific inquiry without satisfactory responses to critics. Clearly, the time has come for the mainstream evolution community to recognize and join the scientific reality of the 21st Century.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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