ORIGINS AND DEMISE OF SELFISH GENE THEORY

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Abstract: *The idea of The Selfish Gene, first published in 1976, grew out of the Modern Synthesis of evolutionary biology formulated by Julian Huxley in 1942, and more specifically from George Williams' Adaptation and Natural Selection in 1966. It presents a severely narrowed down version of Huxley's synthesis, which developed in the 1960s following the formulation of the Central Dogma of molecular biology by Francis Crick. The idea rests on three assumptions: the isolation of the genome from any influences by the soma and its development in interaction with the environment (the Weismann Barrier), one-way causation from DNA to proteins (The Central Dogma), and the auto-replication of DNA (Schrödinger's aperiodic crystal). All three of these assumptions have now been shown to be incorrect. The 'replicator' (DNA) is not independent of the 'vehicle', the organism itself, so that The Selfish Gene can no longer be regarded as a valid scientific hypothesis.*

1. Introduction: the First Debate

When his book *The Selfish Gene* appeared in 1976 (1), Richard Dawkins took part in a debate at the Graduate Centre of Balliol College in Oxford University. One of us (DN) had arranged the event in the charming 16th century Manor House at the core of the Graduate Centre. The other author (RN) travelled from Edinburgh, where he worked on the somatosensory system. There was a specific reason for our keen interest in what Richard Dawkins would say. Both of us had studied Zoology and Comparative Anatomy as undergraduates. DN had been a medical science student at UCL in the 1950s under J Z Young, the renowned anatomist and comparative zoologist (2, 3). RN was a Zoology student at Manchester

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University in the 1970s, where one of his tutors was the gene-centred behaviourist Robin Baker, author of *Sperm Wars: Infidelity, Sexual Conflict and Other Bedroom Battles* (4).

The two-decade difference is significant because, as our article will show, it spans the period when standard evolutionary biology hardened into the Selfish Gene version. Moreover, RN recalls opposing his zoology tutors on the genetic basis of behaviour, particularly its fixed algorithmic nature. Thus, we both encountered and argued about the selfish gene idea before Dawkins' book appeared.

That is not surprising since gene-centrism entered biological research well before *The Selfish Gene*. Julian Huxley's *Evolution. The Modern Synthesis* (5, 6), first published in 1942, provided the general neo-Darwinist background, which rapidly became the standard school teaching of evolution (7). George Williams in 1966 (9) then clearly laid out the specific ideas of Selfish Gene theory in his book, *Adaptation and Natural Selection*.

Williams described a form of mechanistic duality,[1] a clear separation between a replicator (genes) and its vehicle (organism), in Williams' words, "genic selection and organic adaptation" (9, p. 124).[2] The selection acted entirely on genes as the replicator, thus stripping the organism of agency in its evolutionary destiny. Organisms became seen as passive bystanders to the results of blind natural selection in developing their structure and function. Crucially, no adaptations created by the organism could pass to the next generation, as if by some principle of prohibition. Thus, while Dawkins did not invent this dualist idea, his *The Selfish Gene* gave it a powerful voice through his colourful writing.

The 1976 Holywell Manor debate involved Dawkins and two philosophers, Anthony Kenny, author of *The Metaphysics of Mind* (10)) and Charles Taylor, author of *The Explanation of Behaviour* (11). Kenny questioned the dualism by putting the question what interprets the replicator: "if all I knew about the English language was its alphabet, surely I would not be able to understand Shakespeare?" Dawkins did not even attempt to address the problem. He replied: "I am not a philosopher. I am a scientist, I am only interested in truth", a mantra he has used to sidestep philosophical questions repeatedly over many years.[3]

2. The Duality of Williams and Dawkins is a Philosophical Idea

Yet, the duality of Williams and Dawkins is primarily a *philosophical* idea, just as was the 'ghost in the machine' dualism of Descartes. Thus, it requires justification. The

[1] We have followed Gould (8, p. 615), in using the term "duality" to distinguish mechanistic duality from Cartesian "dualism", but, as our article shows, mechanistic duality shares some problems with Cartesian dualism.

[2] The full quote is "We must always bear in mind that group selection and biotic adaptation are more onerous principles than genic selection and organic adaptation."

[3] Precisely that statement was repeated in the debate between Rowan Williams (then Archbishop of Canterbury) and Richard Dawkins, chaired by Anthony Kenny in Oxford in 2012: https://www.youtube.com/watch?v=bow4nnh1Wv0.

question this article addresses is how such a successful book, selling in millions, could have been allowed to sidestep the central philosophical question about any form of dualism: why. Just as Descartes' soul-body separation is unnecessary, so too is that of the vehicle-replicator. There is no need for an organiser (director) within the organiser (enterprise).

The problematic philosophical questions about the mechanistic duality of *The Selfish Gene* were either missed or appeared to be irrelevant. The extraordinary achievements in molecular biology, not least the structure of DNA, gave the sense of solid ground: the 'code' or 'secret' of life appeared to be laid bare. All that was necessary was to unravel it, to open its pages like a book. But three other ideas were erroneously taken as established scientific facts: the one-way causation interpretation of the Central Dogma of molecular biology, the Weismann Barrier, and DNA replicating like a crystal. The first contended that the DNA was read-only and unchangeable by the organism. Thus, it was "sealed off from the outside world", as Dawkins expressed it (1, p. 21). The second was assumed to protect the germ-line cells from carrying any information from the soma in addition to the genes, while the third made it appear that DNA could alone "create us body and mind" (1) and so be the "secret of life" (12). None of this had any empirical foundation. All of it was assumption. It simply had to be so for the gene-centric view to hold.

So, the duality of *The Selfish Gene* is the complete separation between the replicator and its vehicle, with strict one-way causation from replicator to vehicle, presented as scientific truth, almost beyond question. It was, of course, still important to know how organisms can *interpret* their DNA for their development and physiological function. The new discipline of genomics took off, slowly at first, but with the idea that somehow science could unravel the 'genetic blueprint', decipher and understand it. By the turn of the century, this had become a political strategy for health. It is the prevailing viewpoint. Yet, this is another fallacy. It isn't how the cell or organism interacts with the genome. Cells use and control the genome; they don't simply wait for instructions from it. Without the cell, the genome can issue no instructions. It is functionally an integral part of the cell and subservient to its needs. The genome is a slave to the cell, not its master. That was the point of Kenny's question about the alphabet, words and Shakespeare, but this question could not be relevant to a gene-centred view of evolution. Thus, science reduced organisms to the transient disposable 'vehicles' for their 'immortal' genes. Physiology became mainly irrelevant in evolutionary theory. This viewpoint differed from Charles Darwin's, an honorary member of The Physiological Society at its foundation in 1876, while T H Huxley was a leading light in its early days.

So, what of the other pillar of the central dogma, the Weismann barrier? It, too, has fallen in the light of empirical evidence. Physiologists are always sceptical about barriers. They tend to be mutable, like the Blood-Brain barrier, which has selective and changeable permeability. Boundaries in physiology are functional and rarely fixed. So it is for the limitations on transmission to the germ cells. They do not isolate the germ-line cells from RNAs, DNAs, proteins, and many other molecules passing across the 'barrier' from the soma. If a barrier exists, it is functional and selective. The assumptions required for the dualistic separation of replicator and or-

ganism are incorrect. So how was such an edifice created, and how did it gain hold of the science? To answer that, we need to consider its history.

3. The original Modern Synthesis was more open than its current popularizations

Julian Huxley's 1942 book (5) pulled together the early 20th-century work on evolutionary biology, creating the Modern Synthesis viewpoint. It was an extraordinary work of scholarship, providing in almost 600 pages a valuable resource for early 20th century discoveries in evolutionary biology. Compared to the rigid *Selfish Gene* viewpoint, it was also a remarkably open view of evolutionary biology. Shapiro & Noble (13) have documented many discoveries neglected or downplayed in widely used *modern* textbooks and popularisations, creating a closed view of biological systems and closing down a much-needed dialogue and further study. Ideas that science should have rigorously tested empirically became a corpus of self-evident beliefs. Yet 80 years ago, Huxley was open to many of those discoveries. We will list just a few he anticipated:

1. He was critical of Weismann's reliance entirely on natural selection since "mutation alone has been shown to be incapable of producing directional change." (6, p. 29).
2. Nor was he fully convinced of the validity of the Weismann Barrier: "the distinction between soma and germplasm is not always so sharp as Weismann supposed." (6, p. 29).
3. He anticipated Gould (14) on punctuated evolution: "abrupt changes of large extent do play a part in certain kinds of evolution in certain kinds of plants." (6, p. 38).
4. He acknowledged the role of hybridization in species evolution (6, p. 147).
5. He acknowledged that the "mutation rate is increased by sudden environmental changes." (6, p. 137)
6. He anticipated the work of Barbara McClintock (15, 16) and James Shapiro (17, 18) in acknowledging chromosome rearrangement in response to environmental stress (6, p. 137).
7. Remarkably, he anticipated the relative failure of genome-wide sequence studies, in showing very small correlations, even to the extent of formulating the polygenic theory of genomics – phenotype correlations when he wrote "every character is dependent on a very large (possible all) of the genes in the hereditary constitution: but some of these genes exert marked differential effects upon the visible appearance." (6, p. 19)

This range of openness to multiple processes in evolution is extraordinary. But there were two key areas where Huxley's mind appeared closed. The first was that inexplicably perhaps, he did not follow up on his doubts about Weismann. The second was that he followed Wallace in rejecting Darwin's interpretation of sexual and other forms of social selection. Any purpose was to be rigorously excluded from

scientific explanations of evolution, so expunging agency or any direction in evolutionary change.

4. The Hardening of 20TH Century Views on the Central Dogma and the Weismann Barrier

In retrospect, there could have been a progressive and constructive development of the Modern Synthesis towards a resolution of the conflict between purposive and non-purposive interpretations of evolution. Had Huxley followed his instincts on Weismann and sided with Darwin against Wallace on sexual selection, the late 20th century moves in the opposite direction might never have happened. So, what prevented Huxley from leading the way on such a progressive and constructive development?

The answer to that question is relevant to the date of the appearance of *The Selfish Gene* in 1976. By then, the interpretations of the significant discoveries of molecular biology had merged into what became viewed as a robust empirical vindication of George Williams' ideas in his 1966 book.

Huxley himself provides the historical clue in his Introduction to the second edition of his 1942 book, published in 1963, just 5 years after Crick (19) had formulated the Central Dogma of Molecular Biology as the one-way process DNA → RNA → protein.

No doubt enthused by Crick's formulation, Huxley wrote:

> I have left to the end the most important scientific event of our times – the discovery by Watson and Crick that the deoxyribonucleic acids – DNA for short – are the true physical basis for life, and provide the mechanism of heredity and evolution. Their chemical structure, combining two elongated linear sequences in a linked double spiral or bihelix, *makes them self-reproducing*, and ensures that they can act as a code, providing an immense amount of genetical "information," together with occasional variations of information (mutations) which also reproduce themselves. Linear constructions of DNA are, of course, the primary structures in the genetic organelles we call chromosomes. (6, p. 614)

Just three years later, Williams (9) published *Adaptation and Natural Selection*, which by his (Dawkins') own account was the most significant influence on his writing of *The Selfish Gene*.

The emphasis in the quoted passage is ours since it is the smoking gun in this story. There are three critical problems, not least of which is the assumption that DNA is a 'code' containing information. This assumption is now engrained in mythology and rarely challenged. So, let's consider what it means. A code is a system of words, letters, figures, or symbols used to represent others, especially secrets. Or, it might be like a code in computing, a set of assembly code, or instructions. DNA is none of this. Remarkable as it is, it is a tool enabling cells to make and do things. It is not a set of instructions. Of course, when we represent DNA or the genome on our pages or a screen, we use letters of the alphabet. In that sense, we are representing DNA in a code. But the DNA itself is not a code. It is not a representation of something, and it certainly is not an instruction manual. The metaphor of DNA as a code or blueprint feeds into the 'ghost' in the machine duality, some-

thing unique that controls and directs life. Yet, life itself is definitively that special something, with an agency to make and do things, for which it uses DNA. Life, as we know it on earth, depends on much that doesn't require DNA.

The point about DNA as a code might be regarded as semantic or a linguistic convenience, but Huxley's passage contains another fundamental problem: a matter of empirical observation; the concept of DNA as a replicator. Whilst DNAs are replicated most wonderfully, they do not do so without help from the cell. They are not self-replicators. A sufficiently exact replication would be impossible with an error rate of around 1 in 10,000 base pairs. Only small RNA viruses can survive that copying error rate, and even then, they rapidly mutate, as we observe during viral pandemics. We now know that cells use an army of proof-correcting troops to reduce the error rate to just 1 in 10 billion. Such a faithful replication is dependent on this error correction (20, 21). Huxley could not have known in 1963 that genomes the length of the human genome would not work without the activity of the living cell. Nor could Schrödinger when he first proposed that the genetic molecule could be a self-replicating crystal in his 1942 book *What is Life?* (22). But the idea of DNA as the self-replicator persisted and became the key to the replicator-vehicle separation, the mechanistic duality.

It is packaged as information in a code that gets passed on in the germ cells.

Another significant push toward the gene-centred view also appeared in Huxley's introduction to the 2nd edition of the Modern Synthesis:

> I must, however, draw attention to the outstanding event in this field, namely the dethronement of the proteins from their biological pre-eminence. It used to be held that life was based on proteins. Today, we know that DNA is the basis of life and its evolution, and that proteins, though essential for its operation, owe their production to the activities of DNA.
>
> (6, p. 607)

This interpretation did not merely 'dethrone' proteins; it left the organism bereft of agency, for proteins are how such agents do things; how we move, talk, feel, and think. DNA does none of this.

But since highly accurate DNA replication depends on the organised activity of the cellular error-correcting proteins, there has to be a two-way interaction between the 'replicator' and its 'vehicle'. Furthermore, the cell controls gene expression. This interaction or integrative function removes the duality. Causation runs both ways, not one-way. That is the real thrust of Kenny's question to Dawkins. We can only ascribe meaning, purpose, and other social attributes at the level of organisation at which such ascription makes sense. A letter is significant in a word; a word has meaning in a sentence, a paragraph, an idea, or a view. Life can be selfish; DNA cannot. This fact is fundamental to understanding the misuse of "selfish" as a metaphor in *The Selfish Gene*. It is precisely when a metaphor can easily elide into the literal sense from which it derives that care must be taken not to confuse the metaphorical and literal uses. Dawkins regularly confuses them with statements like "we are born selfish" Dawkins (1, p. 3). Dawkins (23) defends his usage of the word as being technical in biology, rather like the use of "spin" and "charm"

in particle physics. But that technical usage in physics is so far from common language that the likelihood of elision into thinking that a particle can really have charm is utterly remote. By contrast, the idea that genes cause selfish behaviour is now so embedded in our culture that it has become the modern version of the theological concept of original sin.

It is the physiological organisation of the living cell, which is a higher-level activity of life, which is necessary for faithful replication. It is also the Trojan Horse at the heart of the Central Dogma. Vehicle and replicator are one. DNA does not 'swarm' within us, controlling us; we use it and maintain it. We can be selfish or selfless in different instances using the same genes or using the same genes to create a piece of music or paint a picture. Nor is a gene selfish because it persists in a 'gene pool'; it might just as readily stay because we are capable of selflessness. The 'gene pool' is us.

Still, the gene-centric view was not fully closed. In 1963, Huxley would not have known what we now know about the process of DNA replication, nor that the way the cell controls its expression and maintains it also provides a way for the cell to alter it. Nevertheless, he was on the right track about Lamarckian forms of inheritance, for he also acknowledged the significant work of Conrad Waddington (24) in showing how genetic assimilation (incorporation) could form the basis of a Lamarckian form of inheritance:

> Meanwhile in Britain, Waddington (1957, 1960) has made a notable contribution to evolutionary theory by his discovery that Lamarckian inheritance may be simulated by a purely neo-Darwinian mechanism. This is called genetic assimilation. It operates through the natural selection of genes which dispose the developing organism to become modified in reaction to some environmental stimulus. (6, p. 580)

It is worth noting that Huxley was not entirely correct. Waddington did not *simulate* the Lamarckian process; he experimentally *reproduced* it since he did the equivalent of the social selection of variants showing the inheritable variation by actively *choosing* the variants to breed from in each generation. It was a strictly Lamarckian process since it was the inheritance of a characteristic acquired through artificial (*i.e.* human) selection. Therefore, it was a model for what animals do through sexual and other forms of social selection (choice). Organisms are active in the natural selection process.

Nevertheless, the quotation shows just how open Huxley was to what came later. It is a historical tragedy that, just when Huxley could have extended his synthesis even more openly, he was thrown off course by what seemed to be irrefutable evidence for the more rigid and closed version of his 1942 Synthesis. This is what led to the frequently quoted mantra that "the Weismann Barrier is now buttressed by the Central Dogma of Molecular Biology".[1] Sadly, Waddington for his sin was excluded from the modern synthesis circle (25).

[1] see *e.g.* "The dogma is a modern version of the Weismann barrier (after August Weismann). This is the principle that hereditary information moves only from genes to body cells, and never in reverse. Hereditary information moves only from germline cells to somatic cells" https://simple.wikipedia.org/wiki/Central_dogma_of_molecular_biology (accessed 18 August 2021).

Before we leave the analysis of why the hardening of the synthesis happened during the 1960s and 1970s, it is important to note two other developments that influenced Huxley in 1963 and greatly encouraged rigidity.

First, many leading scientists still thought that eugenics was a natural consequence of the Modern Synthesis. Huxley wrote:

> It is also clear that, in so far as immediate threats to human progress are overcome, such as over-population, atomic war, and over-exploitation of natural resources, eugenic improvement will become an increasingly important goal of evolving man. (6, p. 587)

Supporters of the Modern Synthesis now avoid reference to how it led to eugenics in the 1930s and 1940s. Sadly, some of the originators of the synthesis were its advocates, however much the holocaust was later denounced. Nevertheless, ethical problems persist in proposals for editing the human germ-line and concepts of 'good' or 'bad' genes. We will return to this question later.

The second development also relates to an outcome of the Second World War. The Soviet Union became the champion of a complete travesty of Lamarck's ideas by generously supporting the work of Lysenko. Huxley makes this clear:

> Only in the U.S.S.R has Lamarckism found favour. Here, under the influence of Lysenko, the peculiar brand of Lamarckism called Michurism was given official sanction, and extravagant and ill-founded claims were made on its behalf, while neo-Mendelian genetics, which everywhere else was advancing in a spectacular way, was officially condemned as bourgeois or capitalist "Morganist-Mendelist" and Soviet geneticists were exiled or lost their jobs. (6, p. 580)

No wonder then that Waddington did not describe himself as a Lamarckian in 1957. It took until 1972-3, when Waddington gave some of the Gifford Lectures in Edinburgh (26, p. 127), for him to admit that his 1957 work demonstrated a Lamarckian process.

This history demonstrates just how much political philosophy influences thought and scholarship. It is not enough to ascribe 'truth' to ideas under a carapace of science.

5. 21ST Century Deconstruction of the Central Dogma and the Weismann Barrier

There were philosophical challenges to *The Selfish Gene* during the 20th century, and those are well-documented in Gould's last magnum opus *The Structure of Evolutionary Theory* (27, chapter 8). These were significant challenges as the extensive influence of the selfish-gene concept in many fields is attributed to the colourful language and use of metaphors for which there has been an assumption of truth. In this section, we will focus on factual errors.

The Music of Life (28) began this process by demonstrating the lack of factual content in the central statement of *The Selfish Gene*:

> Now they swarm in huge colonies, safe inside gigantic lumbering robots, sealed off from the outside world, communicating with it by tortuous indirect routes, manipulating it by

remote control. They are in you and me; they created us body and mind; and their preservation is the ultimate rationale for our existence. (1, p. 21)

The absence of factual content was shown by simply reversing the meaning of each sub-clause to read:

Now they are trapped in huge colonies, locked inside highly intelligent beings, molded by the outside world, communicating with it by complex processes, through which, blindly, as if by magic, function emerges. They are in you and me; we are the system that allows their code to be read; and their preservation is totally dependent on the joy we experience in reproducing ourselves. We are the ultimate rationale for their existence. (28, p. 12)

Except for the trivially true factual statement "they are in you and me", which is the same, no experimental test could distinguish between the diametrically opposing phrases. Dawkins admitted as much in *The Extended Phenotype* (23) when he wrote "I doubt that there is any experiment that could prove my claim". Yet, we can trace a dogmatic gene-centric position back to Weismann, who made the same claim of certainty for his Barrier concept. He wrote, "We accept it….simply because we must, because it is the only plausible explanation that we can conceive." Remarkably, he also admitted that it was not possible to observe the process in detail, so there could be no experimental proof, but continued:

It does not matter whether I am able to do so or not, or whether I could do it well or ill; once it is established that natural selection is the only principle which has to be considered, it necessarily follows that the facts can be correctly explained by natural selection. (29)

Huxley was not alone in criticising Weismann. One of the strong supporters of The Modern Synthesis, John Maynard Smith, wrote in 1998:

it is not clear why he thought it [Weismann's claim that the germ line is independent of the soma] was true. (30)

The absence of empirical evidence is also in Julian Huxley's work. Noble (28) shows that the selfish gene idea is not a physiologically testable hypothesis since the characterisation of the central entity in *The Selfish Gene* as what persists is not independent of the only test of the theory, which is the frequency of occurrence in the gene pool. As Dawkins says "Genes can be counted and their frequency is the measure of their success." (31, p. 346). How else could persistence be measured other than by measuring such frequencies?

In 2011 one of us also noted that

accurate replication of DNA is itself a system property of the cell as a whole, not just of DNA. DNA on its own is an extremely poor replicator. (32, p. 1012)

Speculation about necessary, dogmatic positions, independent of factual evidence, is a *philosophical* position requiring justification. Claims by scientists to deny being philosophers are then self-defeating.

6. The 40TH Anniversary Edition of *The Selfish Gene:* The Last Stand?

2016 was the 40th anniversary of the original publication of *The Selfish Gene* in 1976. As a result, a reprint (31) was issued together with an extensive Epilogue. There are several highly significant facts about this reprint.

First, the original 1976 version is reprinted in its entirety with no revisions. As Dawkins himself comments

> So many exciting things are fast happening in the world of genomics, it would seem almost inevitable – even tantalizing – that a book with the word 'gene' in it would, forty years on, need drastic revision if not outright discarding. (31, p. 345)

Indeed so. So why are there no revisions? Dawkins' answer is

> This might indeed be so, were it not that 'gene' in this book is used in a special sense, tailored to evolution rather than embryology. (31, p. 345)

Precisely so. Dawkins' 'gene' is constructed in such a way that, as we have shown, his thesis apparently has no empirical content.

It is a clever and beguiling tale. It comes equipped with a central character, the gene, selfishly enslaving the organism for its end to maintain its existence. Its objective is a fairy-tale land called the gene pool. But what is this gene? It is whatever it is that makes the story definitively true. It is whatever is inherited, both cause and effect. But it is founded on an illusion. R*egardless of the definition of a gene*, it all depends critically on whether the Weismann Barrier exists, whether DNA self-replicates "like a crystal", and whether the Central Dogma keeps the genome isolated. All three of those assumptions are false. The organism awakes and can make decisions. It can even write a book called "The Selfish Gene".

As a prelude to the quotations above, Dawkins muses

> In some ways I would quite like to find ways to recant the central message of *The Selfish Gene*. (31, p. 345)

We conclude that Richard Dawkins can now rest in peace: the way to recant is to acknowledge that the three foundation stones of the book have gone. They are presumed rules that are now seen to be broken. Furthermore, the facts that have removed those cornerstones inevitably present ethical problems since we can no longer assume that the germ-line is "sealed off from the outside world." Dawkins (1, p. 21).

7. The Ethics of Germ-line Modification

The ideas of the modern synthesis have been adopted and taken for granted in a wide variety of fields, ranging from economics (33) to sociology (34), and, notably, the implications for clinical medicine.

The gene-centred view insidiously affects dialogue in ethics. It has entered our culture as 'truth', a given, and it invades our language. Phrases such as "It is in our

DNA" are now loosely used, often without question of its real meaning or significance. We speak of genetics as a golden bullet for health and well-being (35). Governments provide considerable resources to unravelling its mystery; for several decades study of organisms suffered from this approach. Systems physiology was relatively starved of the resources it needed unless it fitted the modern synthesis.

Had the germ-line really been "sealed off from the outside world" in a way that prevents changing the genome through the actions of organisms or through the deliberate editing of germ-line genomes by clinical intervention, then the ethical problems created by Selfish Gene theory would have at least have been limited in scope in clinical practice. The demise of the theory creates at least three sets of ethical issues arising from the fact that genomes can be edited both by organisms themselves and by us as humans with genetic engineering of the germ-line and diagnosing potential genetic influences in embryos.

7.1. *Gene Therapy*

One of us has already highlighted the ethical dilemma for germ-line gene therapy in humans:

> The major concern with germ-line therapy remains the potential unseen and long- term consequences. We know very little of the way in which mutations might produce both harms and benefits. Genes that might be harmful in one set of circumstances might confer an advantage in another. The classic example is the higher resistance to malaria for heterozygote carriers of the sickle-cell gene mutation. Balanced selection maintains more than one variant of a gene in the population as a result of both the harms and benefits they confer in different circumstances. Another classic example of this in biology would be *Biston betularia*, the peppered moth, which has both dark and white polymorphic states that confer selective advantage or disadvantage in relation to the background. To manipulate the germ-line with insufficient knowledge of long- term consequences would be a high-risk strategy (36).

The possibility of germ-line therapy is still a high-risk strategy and we suspect it will remain so. The polygenic or even omnigenic nature of most diseases makes it impossible to predict all the possible consequences of editing the germ-line since this would involve indefinitely long trans-generational effects. We still know only a modest amount about the many factors involved in the environmental and social impacts on health and disease (37, 38), any of which could also influence the germ-line since it is not protected by a fixed barrier but by a functional and selective process.

7.2. *Diagnosis and Informed Consent*

This is true not only for Germ-line therapy. Even just pre-implantation genetic diagnosis on embryos, which could be used to advise parents of potential genetic risks, opens a Pandora's box of problems, largely concerning the fact that in most cases even the clinical practitioner would not know how best to advise parents:

> The extension of preimplantation genetic diagnosis raises practical ethical issues involving relative burdens, duty of care, freedom of choice, distributive justice, and informed consent. This paper argues for caution in advocating reproductive methods that are costly, have limited chances of success, and for which the long-term outcome is unknown (39).

7.3. *The Non-dualistic Nature of Organisms and Their Interactions with the Environment*

Organisms are necessarily open systems. They mesh with their environment, including other organisms with which they interact, in a multitude of ways. It is strictly impossible to unravel the multitude of interactions between nature and nurture, or indeed any other dualist approach. When causality takes the form of If X and Y then Z we cannot assume that the effects of X & Y can be added linearly. Physiological regulatory networks (often called gene regulatory networks) are adept at managing even when major genetic components are missing. In this sense organisms are robust. This is another reason why it is difficult to predict the outcome of gene therapy.

8. The End of Unnecessary Dualism in Biology

Dualism is a repeating problem in the history of biology. Descartes famously adopted this approach by inventing the 'ghost in the machine', a separate immaterial soul that was thought to be responsible for agency and will in humans. Animals were not thought to be anything more than automata.

The Williams-Dawkins duality is not itself immaterial. It is formulated in a material sense by hiving off a small part of the physical properties of an organism as the centre of organisation from which the whole organism develops. Descartes had the same idea, as he made clear in his *Treatise on the Fetus*:

> If one had a proper knowledge of all the parts of the semen of some species of animal in particular, for example of man, one might be able to deduce the whole form and configuration of each of its members from this alone, by means of entirely mathematical and certain arguments, the complete figure and the conformation of its members.[1]

Furthermore, by making the duality material, the Williams-Dawkins duality leads yet again to a form of Cartesian immaterial soul restricted to human beings:

> Let us understand what our selfish genes are up to, because we may then at least have the chance to upset their designs, *something which no other species has ever aspired to*.
>
> (1, p. 3)

There is no explanation of how this upsetting of physical processes could happen through the immaterial will of humans, nor why the ability is ascribed only to one species. The muddle becomes even worse when immaterial attributes such as 'selfish' and 'immortal' become ascribed to bits of DNA. All such attributions are simply meaningless if interpreted literally; and very misleading when interpreted metaphorically, because the metaphorical and literal meanings are so close as to be easily confused.

[1] The French text reads «Si on connoissoit quelles sont toutes les parties de la semence de quelque espèce d'Animal en particulier, par exemple de l'homme, on pourroit déduire de la seul, par des raisons entierement Mathematiques et certaines, toute la figure et conformation de ses membres;» (*de la formation du fœtus*, para LXVI p. 146; https://archive.org/stream/lhommeetlaformat00desc#page/146/mode/2up).

There *are* immaterial factors that influence the behaviour of organisms. But those immaterial factors are necessarily social properties of whole organisms in their interactions with other organisms. The ways in which that happens require a multi-level analysis of biological organisation (40, 41). Meaning and purpose, including selfishness, can only be ascribed at levels of organisation at which they are appropriate.

9. Conclusion

The Selfish Gene is the best selling science book of the 20th century. But as this paper has shown, *The Selfish Gene* got cause and effect backwards, assigning agency to natural selection instead of the organism itself (41, 42, 43, 44). It embraced the greatest errors of the Modern Synthesis (20, 21) while downplaying much of what it got right (5). It crowned the gene king of biology, even though genes are only servants of the cell (28). Gene-centric duality caused genomics to promise (45, 46)[1] far more than it could or ever can deliver since it cannot distinguish between correlation and functional causation (47). That failure has been at great cost to health care by promising miracle genetic cures that have not met the greatest challenge to health services for ageing populations caused by complex multi-factorial diseases that cannot be reduced to genetic causation (48).

Thus did *The Selfish Gene* turn Neo-Darwinism into a pop religion with its own dogmas, dressed up as science, but without the gold standard of a scientific hypothesis: an empirical test independent of the central assumption of the theory (32). To challenge its rigid dogmas was considered heresy, so that many science careers were lost by those who questioned it. Their discoveries were ignored or, at best, sidelined (49). These misunderstandings have set back treatments in cancer and infectious diseases by many decades (13, 49, 50). This is why *The Selfish Gene* is one of the greatest mistakes in the history of science.

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References

1. Dawkins RD. *The Selfish Gene*. Oxford: Oxford University Press; 1976.
2. Young JZ. *The Life of Vertebrates*. Oxford: Oxford University Press; 1950.
3. Young JZ. *The Life of Mammals*. Oxford: Oxford University Press; 1957.
4. Baker R. *Sperm Wars: Infidelity, Sexual Conflict and Other Bedroom Battles*. London: Fourth Estate; 1996.
5. Huxley J. *Evolution: The Modern Synthesis*. Oxford: Oxford University Press; 1942.

[1] Collins (45) claimed that human genome sequencing would lead to "previously unimaginable insights, and from there to the common good [including] a new understanding of genetic contributions to human disease and the development of rational strategies for minimizing or preventing disease phenotypes altogether."

6. Huxley J. *Evolution: The Modern Synthesis*. Reprint with Introductions to 2nd and 3rd editions and Commentary by Pigliucci and Mueller. MIT Press; 2018.
7. Grove AJ, Newell GE. *Animal Biology*. London: University Tutorial Press; 1947.
8. Gould SJ. *The Structure of Evolutionary Theory*. Harvard; 2002.
9. Williams GC. *Adaptation and Natural Selection*. Oxford: Oxford University Press; 1966 (reprinted as a Princeton Science Library paperback in 2018).
10. Kenny AJP. *The Metaphysics of Mind*. Oxford: Oxford University Press; 1989.
11. Taylor C. *The Explanation of Behaviour*. London: Routledge; 1964 (reprinted 2021).
12. Crick FH. *The Astonishing Hypothesis: The Scientific search for the Soul*. Scribner reprint edition; 1995. ISBN 0-684-80158-2
13. Shapiro JA, Noble D. *What prevents mainstream evolutionists teaching the whole truth about how genomes evolve?* Progress in Biophysics and Molecular Biology. 2021; https://www.sciencedirect.com/science/article/pii/S0079610721000341
14. Gould SJ. *Punctuated equilibrium and the fossil record*. Science. 1983; 219 (4584): 439-440; https://pubmed.ncbi.nlm.nih.gov/17742803/.
15. McClintock B. *The significance of responses of the genome to challenge*. Science. 1984; 226; 792-801.
16. McClintock B. *Discovery and Characterization of Transposable Elements: The Collected Papers of Barbara McClintock*. New York: Garland; 1987.
17. Shapiro JA. *Natural genetic engineering in evolution*. Genetica. 1992; 86: 99-111. doi:10.1007/BF00133714. PMID 1334920.
18. Shapiro JA. *Evolution. A view from the 21st century*. FT Press; 2011.
19. Crick FH. *On protein synthesis*. Symp Soc Exp Biol. 1958; 12: 138-163. pmid:13580867.
20. Noble D. *The Illusions of The Modern Synthesis*. Biosemiotics. 2021; 14: 5-24; https://doi.org/10.1007/s12304-021-09405-3.
21. Noble D. *What future for evolutionary biology? Response to Commentaries on "The Illusions of the Modern Synthesis"*. Biosemiotics. 2021; https://doi.org/10.1007/s12304-021-09448-6
22. Schrodinger E. *What is Life?* Cambridge: Cambridge University Press; 1942.
23. Dawkins RD. *The Extended Phenotype. The Gene as the Unit of Selection*. Oxford and San Francisco: Freeman; 1982.
24. Waddington C. *The Strategy of the Genes*. London: Allen & Unwin; 1957.
25. Peterson EL. *The Excluded Philosophy of Evo-Devo? Revisiting Waddington's Failed Attempt to Embed Alfred North Whitehead's 'Organicism' in Evolutionary Biology*. History and Philosophy of the Life Sciences. 2011; 33: 301-320.
26. Kenny AJP, Longuet-Higgins HC, Lucas JR, Waddington CH. *The Nature of Mind. Gifford Lectures 1971-1972*, Edinburgh: Edinburgh University Press; 1972.
27. Gould SJ. *The Structure of Evolutionary Theory*. Cambridge, MA, and London, UK; Harvard University Press; 2002.
28. Noble D. *The Music of Life*. Oxford: Oxford University Press; 2006.
29. Weismann A. *Die Allmacht der Naturzuchtung* (*The All-Sufficiency of Natural Selection: A Reply to Herbert Spencer*). Contemporary Review. 1893; 64: 309-338; 596-610.
30. Maynard Smith J. *Evolutionary Genetics*. Oxford: Oxford University Press; 1989; ISBN 0-19-850231-1.
31. Dawkins R. *The Selfish Gene*. 40th Anniversary edition. Oxford: Oxford University Press; 2016.
32. Noble D. *Neo-Darwinism, the Modern Synthesis, and Selfish Genes: are they of use in physiology?* Journal of Physiology. 2011; 589: 1007-1015.
33. Lee Y-H, Mayer C, Noble D, Vines D. *Against the microfoundation hegemony: Cooperation in biology, business and economics*. Theoretical Biology Forum. 112; 2019: 53-77.

34. Bliss C. *Social by Nature. The Promise and Peril of Sociogenomics*. Palo Alto, CA: Stanford University Press; 2017.
35. Rose S, Rose H. *Genes, Cells and Brains*. Random House: Verso; 2012.
36. Noble R, Rodeck CH. *Ethical Considerations of Fetal Therapy*. Clinical Obstetrics and Gynaecology. 2008; 22: 219-231.
37. Inskip HM, Godfrey KM, Robinson SM, Law CM, Barker DJP, Cooper C. and the SWS Study Group. *Cohort Profile, The Southampton Women's Survey*. International Journal of Epidemiology 2006; 35: 42-48.
38. Noble R. *Developmental origins of health and disease: Ethical and social considerations*. In P. Gluckman & M. Hanson (Eds), *Developmental Origins of Health and Disease*. Cambridge: Cambridge University Press; 2006: 472-480; doi:10.1017/CBO9780511544699.037.
39. Noble R, Bahadur G, Iqbal M, Sanyal A. *Pandora's box: ethics of PGD for inherited risk of late-onset disorders*. Reproductive BioMedicine Online. November 2008; 17, Suppl. 3.
40. Noble R, Tasaki K, Noble PJ, Noble D. *Biological relativity requires circular causality but not symmetry of causation: So, where, what and when are the boundaries?* Front. Physiol. 2019; 10: 827.
41. Noble R, Noble D. *Can reasons and values influence action: How might intentional agency work physiologically?* Journal of the General Philosophy of Science. https://doi.org/10.1007/s10838-020-09525-3; 2020.
42. Noble R, Noble D. *Was the Watchmaker Blind? Or was she one-eyed?* Biology. 6; 2017: 47.
43. Noble R, Noble D. *Harnessing stochasticity: How do organisms make choices?* 2018. Chaos. 2018; 28: 106309.
44. Noble D & Noble R. *Rehabilitation of Karl Popper's ideas on evolutionary biology and the nature of biological science*. In *Karl Popper: His Philosophy and Science*. (Eds Parusnikova Z. & Merritt D.) Springer-Nature. 2021: 193-210.
45. Collins FS. *Shattuck lecture-medical and societal consequences of the human genome Project*. New England Journal of Medicine. 1999; 341: 28-37.
46. Plomin R. 2018. *Blueprint: How DNA Makes Us Who We Are*. Cambridge, MA, The MIT Press; 2018.
47. Noble D, Hunter P. *How to link genomics to physiology through epigenomics*. Epigenomics. 2020; 12: 285-287; doi: 10.2217/epi-2020-0012.
48. Baverstock K. *Polygenic scores: Are they a public health hazard?* Progress in Biophysics and Molecular Biology. 2019; 149: 4-8.
49. Shapiro JA, Noble D. *What prevents mainstream evolutionists teaching the whole truth about how genomes evolve?* Progress in Biophysics and Molecular Biology. 2021; https://www.sciencedirect.com/science/article/pii/S0079610721000341.
50. Paneth N and Sten HV. *Human Molecular Genetics Has Not Yet Contributed to Measurable Public Health Advances*. Perspectives in Biology and Medicine. 2018; vol. 61 no. 4: 537-549. Project MUSE, doi:10.1353/pbm.2018.0063.