Commentary

Do We Understand Heredity and Evolution? No

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Genetics has been the cornerstone for understanding life for over a century, how it reproduces and evolves, and how human health is sustained. Johannsen's 1911 genotype conception, that 'genes are the units of heredity,' replaced the phenotype conception upon which Galton's successful 1897 law of ancestral heredity was based[1]. However, the case is far from being closed.

In 1992, radiation-induced genomic instability and the bystander effect challenged the genotype conception[2]. Further, in 2009, genetic variance could not explain the fitness trajectory of the *E. coli* bacteria in the Long-Term Evolution Experiment (LTEE)[3]. In 2013, it was clear that evolution in the LTEE was thermodynamically, not genetically, driven[4].

This paper briefly outlines the history of heredity from 1880 and Mendelism from 1900 and reviews recent empirical evidence that fundamentally challenges those two domains. Although in the past century genetics has moved on to encompass such disciplines as epigenetic inheritance, genetic regulatory networks, system biology, etc., 20th century gene-centric concepts of heredity remain foundational.

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1. Introduction

This commentary proposes a reinterpretation of heredity and evolution based on historical perspectives and contemporary empirical observations. It does not present new experimental data but aims, through stimulating debate, to determine whether the contemporary understanding of the scientific foundations of heredity and evolution is valid.

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In 1992, two significant phenomena were uncovered, namely genomic instability[2] and the radiation bystander effect[5]. These findings violate Johannsen's genotype conception, which posits that phenotypic transitions result from genotypic changes. The publication of these papers spurred intensive research on the 'non-targeted' effects of radiation and other environmental stressors from 1995 to 2012. Both effects are now well established *in vitro* and *in vivo,* rendering molecular genetics and the genetic regulation of the cell[6] at least incomplete, if not invalid.

In 2021, Baverstock[7][1], through a reinterpretation of the Long-Term Evolution Experiment (LTEE)[8], showed that genetic variance in the form of acquired mutations could not account for the trajectory of fitness with generation number. He concluded that:

i. evolution was not driven by genetic variance but is rather a thermodynamic process,
ii. that genes were not Mendel's units of heredity, and
iii. that the cell was epigenetically regulated by the cellular phenotype[2], the metaphor for which was a 'brain'.

As these conclusions were contentious, the journal editor invited fifteen researchers criticised in Baverstock's paper to submit commentaries; none did, so the above conclusions remain unchallenged.

When established dogma is criticised, the scientific process requires that such criticisms are either rebutted or the *status quo* is abandoned in favour of new directions of research incorporating the new findings. In this case, a fundamental revision of how the cell works is called for. Baverstock and Rönkkö have made such a proposal[9].

In case there is doubt as to the validity of the above three conclusions, here I briefly review the historiography of inheritance to show that Galton's law of ancestral inheritance[1], which was abandoned in favour of Mendelism, (1) provides a sound description of the heredity process, (2) that Mendelism was not accepted as the result of a sound scientific evaluation of its integrity, and (3) Johannsen's pure line experiments[10] with the haricot bean do not validate the genotype conception.

It is argued that the failure to rebut the three conclusions without any attempt to incorporate the findings into a new paradigm for how the cell works is 'failed science'.

2. A brief and selective historiography of the foundations of heredity 1880 to 1906

There is no intention to provide here a comprehensive account of the relevant events that took place in those 26 years, as numerous historians have written accounts from several perspectives, including[11][12][13][14].

2a. The Law of Ancestral Heredity

Darwin's cousin, Francis Galton, pioneered the application of statistics to biology, particularly in the context of heredity. He proposed a theory of heredity in 1876 (Galton 1876), addressing the phenomenon of regression to the mean (Galton 1886). In 1889, he published *Natural Inheritance* (Galton 1889). In 1897, he published the law of ancestral inheritance, in which he proposed average contributions to the phenotype/traits/characteristics of an offspring made by several generations of the parent's ancestors[1]. This law is based on the direct transmission of phenotype/traits/characteristics and, as noted by Pearson and others in 1903[15], is a description of the inheritance process rather than a biological theory. The law of ancestral heredity serves two purposes: a) as the inclusion of data on the ancestors of the direct parents of the offspring improves the predictability of the law, it confirms the importance of ancestors in the process of inheritance, and b) the law allows for the prediction of the phenotype/traits/characteristics of offspring in terms of probabilities with a reasonable degree of accuracy. The law is based on the study of human families and the breeding records of horses and hounds, applying quantitative and qualitative features such as adult human height, eye and hair colour, and, in animals, features such as coat colour.

At the same time, Galton was working on a theory of heredity based on Darwin's theory of Pangenesis, which he called 'the hypothesis of parts' involving the transfer of 'stirp' via germ cells. According to Bulmer[16], Galton believed that the statistical law and the germ cell mechanism were mutually compatible, citing Galton as saying:

> 'The person may be accepted on the whole as a fair representative of the germ, and, being so, the statistical laws which apply to the persons would apply to the germs also, though with less precision in individual cases.'

Bulmer concludes:

> ‘Thus Galton had come to believe in 1897 that the ancestral law was a logical necessity which could be derived by ***a priori*** arguments, although it required empirical verification.’[16]

2b. The Birth of Mendelism

In 1900, Mendel’s 1866 publication of his work with peas (*Pisum sativum*), from which he derived the principles (later designated as laws) of dominance and segregation, became available due to its republication by Hugo de Vries, Carlo Correns, and Erich von Tschermak. British biologist William Bateson quickly recognised its value and became Mendel’s foremost advocate in England. Olby[17] describes in detail how Bateson introduced Mendelism in England, with a lecture to the Royal Horticultural Society of London and with his book *Mendel's Principles of Heredity – a Defence*[18]. However, Olby notes:

> ‘Even Mendel's three “rediscovers” had serious doubts about the extent of application of Mendel's laws and one of them, De Vries, as Onno Meijer has shown, started to belittle Mendelian heredity within a year of introducing so dramatically the triple 'rediscovery''.[17]

WFR Weldon was quick to use the newly founded biometric journal, *Biometrika,* to draw attention to contemporaneous experimental work that did not support the law of dominance[19]. This was the start of the well-known dispute between the Mendelians and the biometricians between 1902 and 1906, which is related by Provine[12]3.

The key to Mendelism ultimately being adopted as the basis for population genetics and evolutionary theory was a meeting of the Zoological Section of the British Association in Cambridge on 18 and 19 August 1904. Following the vigorous and fractious debate, with Weldon accusing Bateson of repeatedly adjusting Mendel’s theory to fit experimental facts[20] and Pearson referring in a footnote in[15] to

> ‘….. observed experience in man, horse and dog which I am unable under any hypothesis to bring under Mendel's "Principles."’,

that preceded the meeting4, it might have been expected that the science of both sides of the argument would have been debated. The report of the Cambridge meeting in the journal *Nature*[21] shows that this was not the case.

A particular issue that deserves attention is the experiment with mice that Weldon had asked his student, A. D. Darbisher, to perform specifically to test Mendelism. According to Provine[12], in 1903, Darbisher wrote to Bateson:

> 'I am absolutely unbiased about Mendel and I'm very keen to come to an unprejudiced conclusion on it.'[12]

At that time, Darbisher interpreted, in his second report, his results on eye colour inheritance as being unsupportive of Mendel's ideas. In January 1904, Darbisher published his final results on the mice experiment, which he considered to be a 'grave challenge to the future of Mendelism".[12] However, in the early part of 1904, Bateson made extensive investigations of Darbisher's results and uncovered inaccuracies in their recording. Darbisher had already irritated Weldon and Pearson by claiming, in a publication in March 1904, that in one case of a hybrid from a cross, he found results more in line with Mendelism than with the biometric expectation. According to Provine, Darbisher wrote to Bateson asking him not to disclose publicly his findings, saying:

> '..... to have my records discredited would be heart-breaking and render it useless and a waste of time for me to go on with the costly experiments I am carrying out now.'[12]

Thus, immediately before the Cambridge meeting in August of that year, Bateson had, at the least, created doubt and confusion in the biometric camp.

Bateson opened the meeting as its chairman with a long discourse on Mendelism, barely mentioning the then-still-standing law of ancestral heredity. An account can be found in the report in *Nature*[21]. On the following day, Weldon presented a critique of Bateson's interpretation of one of Mendel's pea experiments with green and yellow-seeded races from which the influence of ancestors might be derived and could thus potentially distinguish between the ancestral law and a Mendelian interpretation. He concluded that 'The description of the seed colours is not accurate enough to enable one to decide between these two hypotheses.'[21]. The *Nature* report includes Darbisher's presentation of his experiments with mice, concluding that 'Some of the facts seem to confirm the Mendelian interpretation, while others may be described in terms of either Galton's or Pearson's formulae of ancestral inheritance.'[21].

It is, therefore, clear that the Cambridge meeting cannot be described as producing a scientific endorsement of Mendelian heredity with a clear superiority over the law of ancestral inheritance. The one experiment designed to test Mendelism, Darbisher's mouse experiment, could be interpreted as

supporting both hypotheses as confirmed by[22] who draws attention to a 'little fable' Darbisher wrote, which remained unpublished until after he died in 1915. It is titled *The Laying Bare of the Marvel: A Legend*. Here Darbisher refers to the gathering of the

> 'priest followers' and the 'life measurers' 'on a certain day' .....
> 'There was also there one Petúrcha... Petúrcha was young; he was not a chief, but he marvelled at the marvel. In the dwelling, at the appointed time, words fell from the mouth of the chief of the priest-followers which were not pleasing to the life-measurers; and that which the chief of the life-measurers said found no favour with the priest-followers; and each party said, "We are right"; and each party said, "You are wrong." But Petúrcha said, "Both may be right," and he found favour neither with the life-measurers nor with the priest-followers.'[22].

Ankeny provides a comprehensive account of Darbisher's scientific life, including a detailed account of the episode referred to above, where Bateson found flaws in Darbisher's records. Writing to Bateson before the Cambridge meeting, Darbisher says

> '..... the mistakes you have discovered are not cases of mistaken identity, but nearly always cases of the different estimations of the nature and colour of a mouse at different times, foolish things to let creep into a paper.'[22].

Bateson refused to meet Darbisher privately (Darbisher was constrained by his loyalty to Weldon, (his supervisor) to resolve the scientific issues, Bateson insisting that

> '..... any communication between us which is to serve as a basis of discussion must be of a public nature.'[12]10.

Darbisher's endorsement of Mendelism (although endorsing the biometric solution as well) at the Cambridge meeting made further opposition to Mendelism by Pearson and Weldon difficult. Weldon commenced a review of the evidence on horses in the *Stud Book* but died on 13 April 1906 before he completed it. 'Pearson mourned the loss of his friend. He was angry that arguing with the Mendelians had taken so much of Weldon's time.'[12]11. Pearson then moved on to other interests, notably eugenics.

Thus, Mendelism, as it were, 'slipped under the fence': there was no scientific evaluation of the merits of the two approaches. Throughout the history of genetics, the theory has been adjusted to agree with data, as noted by Norwegian geneticist Stig Omholt[23]:

> ‘Since Gregor Mendel gave us the concepts dominance and recessivity more than 140 years ago (Mendel, 1866)[12], geneticists have invented several additional concepts to describe statistically inferred patterns in their data, like gene action, heritability, epistasis, heterosis, penetrance, expressivity, GxE interaction, pleiotropy and canalization. All these concepts are in active use in production biology, evolutionary biology and medicine, and in terms of underlying mechanisms they are all far from well understood.’[23][13].

Despite Bateson’s efforts (some unprofessional), he was not able to endow Mendelism with scientific credibility.

2c. The genotype conception

In 1911, Wilhelm Johannsen published his paper, *The Genotype Conception of Heredity*[10], discussing the results of his pure line breeding experiments with *Phaseolus vulgaris* carried out in 1901/02 and reported in detail in a book in the German language in 1903[24]. The genotype conception, whereby inheritance of the genotypes in the parental gametes determines the phenotype of the offspring, underpins genetics today. In his 1911 paper, Johannsen emphatically rejects heredity by the direct transmission of phenotypes[14], the basis for the biometricians’ approach. He also rejects any influence of ancestors in heredity[15]. Both of these are important features of the biometric approach.

The pure line breeding approach had been pioneered some years earlier by French breeder Louis de Vilmorin. In 1901, Johannsen sowed haricot beans he had bought in the market (F0), isolating each plant from pollination by its neighbours and produced 19 self-fertilised pure lines/types, each line having a characteristic average weight of its progeny beans (F1), harvested in the same year. In 1902, he weighed a selection of these beans of differing individual sizes and sowed them, assigning their phenotype to be their individual weights and, as before, keeping the lines separate and the plants isolated from pollination by other plants. He harvested their progeny (F2) that same year.

He published the detailed results in 1903[24]. According to Norwegian historian Nils Roll-Hansen[25], Johannsen was surprised that the F2 beans had a phenotype characteristic of their line/type, and unrelated to the phenotype he had assigned the F1 beans as parents, indicating that selection was not possible from pure lines. In his 1989 paper, Roll-Hansen calls Johannsen’s experiment “crucial”, but this is not about its confirmation of the genotype conception but about the long-running parallel issue of whether variation was continuous, as Darwin and the biometricians had proposed, or discontinuous, as

de Vries had proposed in his Mutation theory[26] and as Bateson and the Mendelians claimed. According to Roll-Hansen, the fact that the variation in Johannsen's F1 beans, which he called *fluctuating variation*, was not heritable confirmed that variation, as it applied to evolution, was discontinuous because it was this kind of variation that the biometricians were claiming to be continuous. By 'crucial', Roll-Hansen means an experiment that distinguishes between competing hypotheses[25], i.e., the continuous/discontinuous variation debate. He sees no dispute between the genotype and phenotype conceptions, as the genotype conception is not discussed in the paper. Roll-Hansen, arguably Johannsen's foremost interpreter, therefore does not attach much importance to the genotype conception.

However, given the success of the law of ancestral heredity, which relies on the direct transmission of phenotypes, it is necessary to examine whether Johannsen's claim that his pure line experiments confirm the genotype conception is valid or not. It is important to note that Johannsen adopted Mendelism, which he claimed supported the genotype conception. He writes:

> 'The genotype conception, initiated by Galton and Weissman [here he is referring to the germline work with stirp by Galton and Keirmplasma by Weismann] but now revised as an expression of the insight won by pure line breeding and Mendelism, is in the least possible degree a speculative conception.'[10].

According to Provine[12]:

> 'Students of heredity found Johannsen's pure line theory and his claim of it to hybrid populations very appealing, especially in America where de Vries' mutation theory was already popular.'

After the presentation of his 1911 paper, Johannsen toured America, lecturing on his pure line theory, which progressively became less criticized.[12]. In a sense, one might say that the genotype conception 'rode to success on the back of Mendelism'.

Johannsen's pure line beans, being produced by self-fertile plants, had identical parental genotypes, and they produced phenotypes typical of their line/type. Johannsen proved that fluctuating variation was not heritable, but his experimental system does not have the power to endorse the genotype conception. Further, ancestry cannot influence the results of his experiments. Thus, his pure line experiments are not capable of saying anything about the process of heredity: the pure line system is too simple for that.

2d. Summary of the historical evidence

Galton and Pearson's law of ancestral heredity has two important merits because it is a good description of the heredity process, namely that it testifies to the influence of ancestral data in the process of heredity, and it can make probabilistic estimates of the phenotypes of offspring based on the phenotypes of parents and ancestors. Nevertheless, it has been rejected in favour of Mentalism since around 1906 despite numerous instances of experimental work failing to agree with Mendel's laws, a continual need since then to adjust Mendel's theory to fit experimental data[23], and a failure to identify the genes, using genome-wide association and the human genome sequence, that are assumed to be responsible for common genetic diseases, e.g., schizophrenia[27].

3. Review of recent evidence regarding Mendelism and the genotype conception

3a. The phenomena of radiation-induced genomic instability and bystander effect

Ionising radiation is well known to induce mutations in DNA and, therefore, the genotypes of organisms, potentially leading to disease phenotypes. However, the above two phenomena indicate that phenotypic changes can be induced in organisms without involving genotypic changes, i.e., in violation of the genotype conception. For example, after irradiation of mouse bone marrow cells with ^{238}Pu alpha particles, karyotypic changes, termed chromosomal or genomic instability, were reported in cells grown as clones over several post-irradiation generations[2]. Also, in 1992, Nagasawa and Little[5] showed the 'bystander effect' in Chinese hamster cells irradiated with ^{238}Pu alpha particles. A dose of 0.31 mGy caused an increase of sister chromatid exchanges in 30% of the cells, while less than 1% of the cells were hit by alpha particles. These effects are also reported in human zygotes and fetuses[28]. The experimental evidence for these phenomena is reviewed by Schoefield and Kondratowicz[29].

Genomic instability and the bystander effect are well established by several international research projects to investigate the so-called 'radiation-induced non-targeted' effects between 1995 and 2012. These effects are also caused by other environmental stressors, such as air pollution. They prove that the genotype conception is not a universal concept, if indeed there are areas of biology in which it does apply. In practice, in sexual reproduction, it is not possible to *prove* that the inheritance of the gamete genotypes is the cause of the offspring phenotype.

3b. The long-term evolution experiment (LTEE)

The 'Long-Term Evolution Experiment (LTEE)' has been running for over 30 years, accumulating more than 70,000 generations of an initially genetically uniform founder population of *E. coli* bacteria across 12 replicate samples[8]. This makes the LTEE an invaluable resource for investigating the evolutionary process. Researchers have published several peer-reviewed progress reports to evaluate the experimental results.

The experiment is designed such that the bacteria consume all available nutrients within 24 hours. Each day, for every replicate culture, an aliquot of the nutrient-deprived bacteria is transferred to a new flask with fresh nutrients. Periodically, researchers measure growth rates (fitness), cell size, and DNA sequences to track mutations (variance). Fitness is defined as the growth rate relative to the founder population.

In 2009, after 20,000 generations, LTEE researchers reported on the relationship between the linear progression of genomic evolution (acquired mutations) and the highly non-linear trajectory of fitness[3]. See Figure 1 below. They were unable to explain this relationship solely through beneficial and neutral mutations.

By 50,000 generations, fitness trajectories across all 12 replicate cultures followed an identical power law. (See Figure 2 below and Figure 2 in[4]). To explain the power law trajectory, LTEE researchers proposed a statistical model invoking "diminishing-returns epistasis" and "clonal interference"[4].

R. A. Fisher's model in *The Genetical Theory of Natural Selection*[30], based on Mendelian genetics, proposed that the rate of change in mean fitness equals the genetic variance of a species. However, Fisher's model applies only to single time points and does not account for mutations. To address this limitation, Basener and Sandford[31] reformulated the model for extended periods. They calculated fitness trajectories based on two distributions of beneficial versus deleterious mutations. Under a Gaussian distribution (equal numbers of beneficial and deleterious mutations), fitness increased at a gradually accelerating rate. With a Gamma distribution (excess deleterious mutations), mean fitness decreased as variance increased. The latter distribution is more realistic.

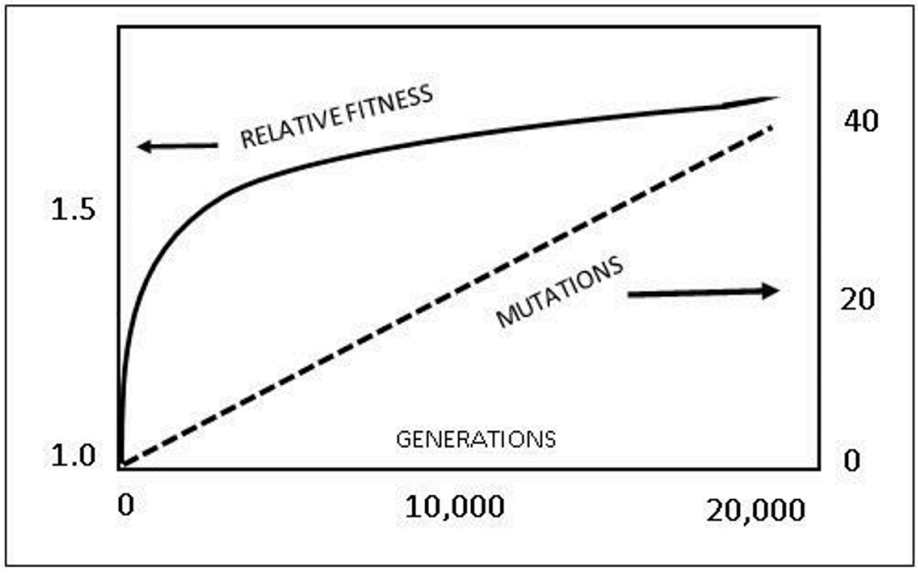

Figure 1. A conceptual diagram depicting the evolution of relative fitness (solid line) and mutations (dashed line) over the first 20,000 generations of the LTEE. While fitness trajectories for all 12 replicates are identical, cell volume trajectories are not superimposable. By 10,000 generations, cell volumes range between 1.5 and 2.5 times the original size[32].

The lack of constant proportionality between genomic and fitness evolution is clear from Figure 1. Thus, the LTEE contradicts Fisher's foundational law and the assumption that evolution is driven solely by genetic variation.

Figure 2 shows the fitness trajectories up to 50,000 generations modelled according to a power law (solid line) and a hyperbolic model (dashed line) based on the extrapolation of fitness data for the first 20,000 generations.[4]

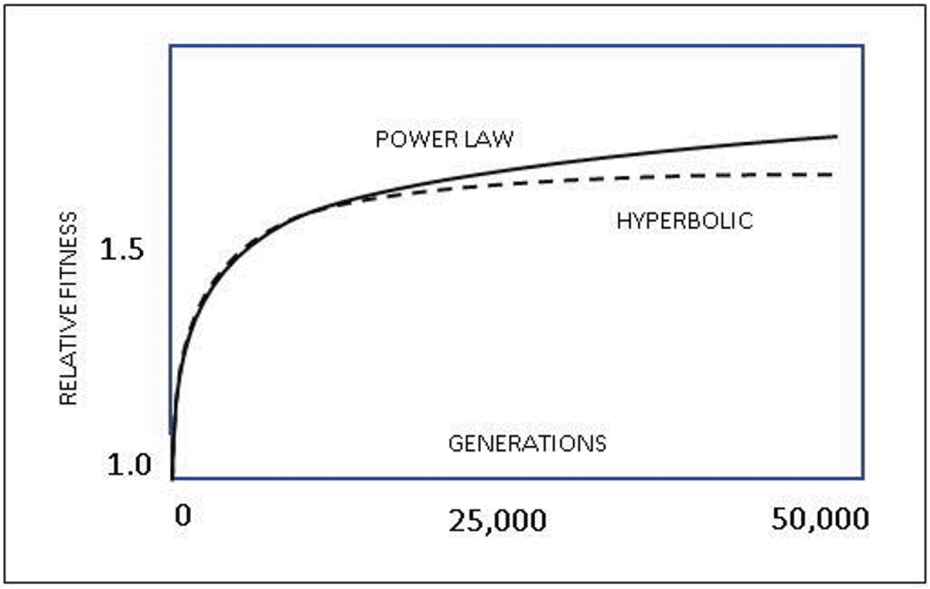

Figure 2. A conceptual diagram comparing power-law and hyperbolic models for fitness trajectories across 10 replicate LTEE experiments. Two replicates were excluded due to hypermutability after 30,000 generations. Extrapolations to 50,000 generations show a superior fit to the power-law model.[4]

From Figure 2 in[4], it is clear that the data from 25,000 to 50,000 generations is compatible with the power law, not the hyperbolic model.

Baverstock[33]16 addresses the question of whether 'diminishing-returns epistasis' and 'clonal interference' can account for the power law dependence of the fitness trajectory, and its independence from the identity of the mutations acquired. He points out that while the fitness trajectories in the 12 replicate cultures are identical, the same is not true for the trajectories of cell size, which vary between replicate cultures. Thus, if 'epistasis' is responsible for the former, it does not apply to the latter. If both trajectories are the result of mutations, then why not? Therefore, as cell size variation is very likely the result of mutations, it may be concluded that fitness depends on something other than mutations. Furthermore, for clonal interference to influence fitness identically in 12 independent replicate cultures, beneficial mutations would have to occur very frequently. In 1998, Lenski concluded, based on evidence from the experimentally determined spontaneous mutation rate of *E. coli*, that one in about a million mutations would be beneficial. Thus, for all 12 replicates to acquire beneficial mutations in the earliest generations (mutations are acquired at a rate of about 4 per 1,000 generations) would have a vanishingly

low probability if they are only one in a million mutations. The above is a summary of the argument presented in[33].

The LTEE thus does not support a direct relationship between genetic variance and the rate of evolution. Instead, the universally observed power-law trajectory aligns with principles of thermodynamics[34][35][36]. This suggests that fitness evolution is a thermodynamic, rather than purely genetic, process.

3c. The evolution of minimised bacteria

Minimized bacteria have had their inessential genes removed through a process known as streamlining. Moger-Reischer et al.[37] report that a genetically engineered *Mycoplasma mycoides* bacterium, streamlined by removing all non-essential genes, evolved at the same rate as the non-minimalized bacterium from which it was derived. The minimized genome was reduced by almost 50%. The fitness, measured as the growth rate of the minimized ancestral bacterium, was 50% of that of the non-minimalized bacterium, and the mutation rates of the two genomes were indistinguishable. However, the rates of fitness increase were similar in both bacteria over 2,000 generations, although the mechanisms of adaptation were divergent. The authors conclude:

> 'Despite reducing the sequence space of possible trajectories, we conclude that streamlining does not constrain fitness evolution and diversification of populations over time.'[37].

This conclusion by the authors is correct, but assuming that evolution is a thermodynamic, not a genetic, process: independence of the rate of adaptation on the size of the evolving genome is expected. If the rate of increasing fitness depended on genetic variance, since the mutation rate per gene is independent of the length of the bacterium, the variance would be less in the non-minimized bacterium, and the rate of fitness increase would be lower. Evolution, as a thermodynamic process, depends on the availability of sufficient free energy (nutrients) to replicate, and under the culture conditions used in this experiment, that condition was met.

3d. Conclusions and implications from recent evidence

A significant body of evidence, mostly acquired since 1990, on genomic instability and the bystander effect, violates the genotype conception in which it is assumed that phenotypic changes require modification of the genotype. Further, the LTEE provides direct evidence to the effect, contrary to Fisher's

Genetical Theory of Natural Selection[30], that evolution is not driven by genetic variance. The power law trajectory of fitness (adaptation) indicates that, like evolution in other natural systems in general, orgasmic evolution is a purely thermodynamic process.

These stipulations imply that although on cell division bacteria inherit their parent's genotype, their genotype does *not* determine their fitness (phenotype). In the context of sexual reproduction, they imply that it is not the genotype that carries the information from the parents that determines the offspring's phenotype, i.e., Mendel's unit of inheritance is *not* the gene.

If not the genotype, then what is passed from parents to offspring? Johannsen saw the phenotype conception as the alternative to the genotype conception, which he rejected because this would involve the inheritance of 'personal qualities' of the organism, which he maintained did not happen.[10]. Omholt[23] addresses the genotype-phenotype relationship required by the genotype conception: i.e., the assumption that the genotype causes the phenotype. Omholt writes:

> 'There is no ***a priori*** reason why an offspring, arising from the random sorting of chromosome pairs plus genetic recombination and the subsequent immense number of highly complex and nonlinear processes making the individual, should on average resemble its parents more than a randomly drawn couple from the population. We have no theory that tells us why this would not give rise to a quite unpredictable parent-offspring relationship.'[23].

However, the facts are that likenesses are transmissible across generations, as exemplified by the characteristic jaw of the Habsburg lineage. The law of ancestral heredity predicts that this will be the case. Thus, it must be accepted that there is some other source of information that is transferred from parent to offspring in addition to their genotypes. This information is responsible for the offspring's phenotype and can include likenesses to parents and ancestors and, as recognized by Galton[16], not necessarily expressed in every intermediate generation.

Numerous organelles in the eukaryotic cell can be transmitted between generations along the female line, most notably mitochondrial DNA, but sperm carry little else than the chromosomes and proteins; yet intergenerational resemblance is not confined to the female line. Logic, therefore, demands that cells, including both male and female gametes, contain another transmissible entity. Baverstock and Rönkkö[9] have proposed that this is a material entity that would be described as a gene product

interactome in today's terminology and embodies the cellular phenotype. It can be seen as a cellular partner to the genotype and the phenotype in its manifestation as a noun.[17]

In sexual reproduction in the IA model, the offspring phenotype is a fusion of the interactomes from the parental gametes. The genotypes are, of course, inherited and undergo genetic recombination but serve to feed gene products to the gene product interactomes rather than define the offspring phenotype.

4. Discussion

In the context of the historical evidence concerning heredity from 1880 to 1911, it is established herein that Galton's law of ancestral heredity is a viable description of the heredity process and that its abandonment after Weldon died in 1906, in favour of Mendelism, as promoted by Bateson, occurred without a proper scientific debate over the relative merits of the two approaches to heredity. The crucial British Association meeting in August 1904[21], presided over by Bateson, was a failure in science, which has turned out to have huge consequences, i.e., the HGP (see below).

It is the contention herein that the above reinterpretation of the LTEE rejects the role of genetic variance in evolution, and hence, Mendelism and the genotype conception are confirmed as false. Further, organismal evolution is deemed not a biological but a thermodynamic process, in line with how natural systems evolve[34][35][36]. As inherited mutations mostly[18] do not influence the offspring, most common diseases do not have a genetic origin, even if family and twin studies suggest they do.

Further, Johannsen's pure line bean experiment does not provide evidence for or against the genotype conception, as heredity in single-parent self-fertilising plants is too simple to illustrate the complexity of sexual reproduction[19]. However, the failure of Mendelism invalidates the genotype conception: genes are not Mendel's units of heredity.

Thus, it must be accepted that heredity and evolution, the most important features of biology, as they are currently perceived, are fatally challenged: we currently have only a statistical description of the process of heredity rather than a comprehensive theory or hypothesis, and, for evolution, no theory or hypothesis as to what drives it. This situation, after a century of research, is part of a broader failure in science, highlighted by physicist Sabine Hossenfelder in the context of fundamental physics[38], which remains unaddressed to this day[20]. The failure in biology is different, but it is important as it pertains to our understanding of public health. The continuing research using the GWA methodology is increasing the

already massive opportunity cost of having adopted Mendelism in 1906. I have argued that the product of GWA studies, i.e., polygenic risk scores, is a public health hazard[39].

The flawed concept of Mendelism led to the Human Genome Project (HGP), which involved sequencing the human genome at a cost of US$3 billion. Subsequent research employed the genome-wide association (GWA) technique to identify genes responsible for specific traits, in particular schizophrenia (SZ), at an additional cost of US$3 to 5 billion[21]. Since the completion of the HGP in 2001, 2,115 English language papers on SZ using GWA have been published, out of more than 50,000 studies mentioning GWA in either the title or Abstract. Many of these papers have appeared in elite journals such as *Nature*, *Science*, *Cell,* and *PNAS*. Despite numerous 'celebrations' of partial success[22], the genes accounting for the roughly 50% of SZ believed to be genetic in origin have not been found.

Focusing on the genetic causes of SZ incurs opportunity costs, depriving other approaches to understanding the trait. For example, Michael Jones and colleagues[40] attribute SZ to trauma in adolescence, with no genetic involvement, i.e., as a social consequence. In reviewing the achievement of HGP in the NIMH SZ programme[41], Torrey concluded that

> '..... three decades later [after the launching of the HGP] NIMH's genetics investment has yielded almost nothing clinically useful for individuals currently affected.'

The reason is clear: genetic diseases are rare[23] because what determines the phenotype of the offspring of a sexual union is not the parental genotypes but their cellular phenotypes[9]. The human genome sequence and the GWA studies are largely irrelevant.

Using the UK Biobank as a source of data on morbidity and mortality, Argentieri et al[42] have attempted to relate these data to potential health-damaging environmental and lifestyle exposures using their concept of an 'exposome', and genetic origins by calculating polygenic risk scores (PRS). They find that the exposome overwhelmingly accounts for the morbidity data, i.e., genetics plays little role in longevity and, by inference, in common diseases.

These studies leave little doubt that assuming the gene is the significant entity transferred from parents to offspring, the genotype conception, gives a false view of heredity. In 2021, I challenged this false view primarily based on a reinterpretation of the LTEE[7]. As the paper was controversial, the journal editor, Denis Noble, invited 45 researchers mentioned in the paper to submit commentaries with a view to

publishing an Online Collection. Only 7 researchers responded. This is what Noble said in his editorial for the Online Collection:

> 'The Editor's role is to try to get opinions and arguments across the spectrum of views and interpretations.
>
> When I received Keith Baverstock's article I therefore acted as any Editor should: take a long view, solicit reactions from a wide spectrum of known opinion and expertise, then sit back and wait for the debate to happen. I therefore invited commentaries from around 15 scientists who I judged would be broadly favourable to the article, while obviously having their own criticisms from their particular standpoint. I also invited around 15 who, from their previous work, would be expected to be strongly opposed to the main thrust of the article, and some who might be in between. An overall total of 45 were invited.
>
> Two years later, in response, the journal has received 7 articles from the first and third group of invitees, but ***none whatsoever*** from the second. Those invitees included leading geneticists and genomics people. Why the silence?'[43]

Noble is unequivocally identifying a failure of the scientific method here: criticism *demands* a response from those criticised, if only for the reason given by Noble, i.e., that taxpayers fund a great deal of research.

A further 2 years later, we can still ask, 'Why the silence?'. Is it that the mainstream genetics and evolution communities do not read the literature? Since 2021, four highly eminent authors have published three books addressing the above topics[44][45][46]. Their titles are, respectively, *How Life Works: A User's Guide to the New Biology*; *The Master Builder* (referring to the cell explicitly, not genes); and *Understanding Living Systems*. All three books explain that the perception of what genes do has changed in the last decade from being viewed as a 'blueprint' for life, for example[47], to a much more passive role, with epigenetic marking and the cell/organism taking over the role that was assumed to be performed by genetic regulatory networks, e.g.,[6].

However, none of the above books mention the LTEE, the genotype conception, or my 2021 claim that it is not the gene that is the 'unit of inheritance' but the cellular phenotype. All three books are uncritical narratives based on the flawed concepts of Mendelism: as such, they are a deafening addition to 'the silence'. Perhaps the biggest mistake, certainly in biology but perhaps in the history of science, is the uncritical acceptance of Johannsen's interpretation of his pure line experiment: the belief in the

correctness of the genotype conception as the ‘mechanism’ underlying heredity. None of the three books mentions this, or Johannsen’s experiment, although Marinez Arias is sceptical of the usefulness of GWA and polygenic risk scores, and Ball analyses the limitations of GWA, but still appears to see a role for the genome in medicine.

My challenge to them is to invite them to rebut my arguments in[7] and further elaborated in sections 2 and 3 of this paper or accept that they are peddling failed science.

5. Conclusions

Both historical and contemporary empirical evidence testify to the currently mainstream bases of the foundational elements of biology, heredity, and evolution being deeply flawed. The failure, despite the investment of between five and seven billion US$ to find genes that are the cause of SZ, should alone be enough to establish the flawed nature of the underlying assumptions of genetics, the invalidity of the GWA methodology, and the irrelevance of the human genome sequence. Science must better understand a) the nature of the law of ancestral inheritance and how it can form the basis for a biological theory of inheritance, b) the cellular phenotype of gametes, and c) the implications of evolution being a thermodynamic process.

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Footnotes

[1] The 2021 version of the paper was corrupted: the corrected version was published in 2024.

[2] The cellular phenotype is the apparatus in the cell that converts the information coded in the genes, notably that which specifies proteins, to the characters that emerge from the cell, e.g., its fate. It is often referred to as a genetic regulatory network. In the Independent Attractor model of the cell, it is assumed to be a gene product interactome. See Introduction to Baverstock, K.[7]. Its origin is described in: Baverstock, K. and M. Rönkkö[9].

[3] See Chapter 3, p. 36.

[4] At one point in 1904, the editor of *Nature* refused to publish any more of Bateson’s submissions-

[5] Page 74

[6] Page 76

[7] Page 79

[8] Page 539

[9] Page 538

[10] Page 79

[11] Page 88

[12] Mendel's paper in English and annotated can be found here: http://www.mendelweb.org/Mendel.html

[13] In his book *How Life Works,* Philip Ball says that Mendelian traits are the exception rather than the rule (see page 60, footnote 6). Ball, P.[44]. He then says that some researchers think that teaching genetics according to Mendel gives a false conception of how genes work. It does appear to cross his mind that a law that is obeyed less than 50% of the time might simply be wrong and that the issue is that genes are not Mendel's units of inheritance.

[14] "The transmission of properties—these may be things owned or peculiar qualities—from parents to their children, or from more or less remote ancestors to their descendants, has been regarded as the essential point in the discussion of heredity, in biology as in jurisprudence. Here we have nothing to do with the latter; as to biology, the students of this science have again and again tried to conceive or "explain" the presumed transmission of general or peculiar characters and qualities "inherited" from parents or more remote ancestors. The view of natural inheritance as realized by an act of transmission, viz., the transmission of the parent's (or ancestor's) personal qualities to the progeny, is the most naive and oldest conception of heredity."

[15] Ancestral influence! As to heredity, it is a mystical expression for a fiction. The ancestral influences are the "ghosts" in genetics, but generally, the belief in ghosts is still powerful. In pure lines, no influence of the special ancestry can be traced; all series of progeny keep the genotype unchanged through long generations. A. D. Darbishire's laborious investigations as to the classical object of Mendel's researches, green and yellow peas, may even convince a biometrician that the ancestral influence is zero in "alternative inheritance." Ancestral influence in heredity is, plainly speaking, a term of the "transmission-

conception" and nothing else. The characters of ancestors as well as of descendants are both in quite the same manner reactions of the genotypical constitution of the gametes in question. Particular resemblances between an ancestor and one or more of his descendants depend—so far as heredity is responsible—on corresponding particular identities in the genotypical constitution, and, as we have urged here, perhaps to excess, the genotype is not a function of the personal character of any ancestor.

[16] Section 2

[17] As defined by Johannsen, and since, phenotype is defined as an adjective. The noun to which it applies in most situations is an organism (e.g., a pink flower). However, the proposed interactome, the attractor states of which give rise to the phenotypic properties, is technically the 'cellular phenotype'

[18] Exceptions are rare inherited monogenic mutations and mutations that appear to predispose for breast cancer and dementia.

[19] This is an issue I raised in Baverstock, K.[7] "The Gene: An appraisal." Prog Biophys Mol Biol **186**: e73-e88. (See page e77)

[20] https://www.youtube.com/watch?v=HQVF0Yu7X24. Also, the German author and physicist Alexander Unzicker has expressed similar views.

[21] Estimate made by CoPilot.

[22] For example, this from the NIH: https://www.nih.gov/news-events/news-releases/schizophrenias-strongest-known-genetic-risk-deconstructed?form=MG0AV3.

[23] Confined to rare inherited monogenic traits and genes that seem to influence diseases such as breast cancer (BRCA1 and 2) and dementia (APOE).

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