The Demise of the Gene

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The gene is losing its luster as a biological explanatory principle, but those who stand to profit from its supremacy are promoting it harder than ever. It is nearly 70 years since the Nobel Prize-winning physicist Erwin Schrödinger wrote: “The chromosome structures are... instrumental in bringing about the development they foreshadow. They are code law and executive power, or to use another simile, they are the architect’s plan and the builder’s craft in one” (Schrödinger 1945). (Another Nobel Laureate, the developmental biologist Sydney Brenner [2001, 34], later called this statement “Schrödinger’s fundamental error.”) It is almost 30 years since still another Nobelist, the cancer biologist David Baltimore (1984), termed DNA the “executive suite” for which the rest of the cell is the “factory floor.”

Studies over the past few decades have thoroughly dispelled these reductionist fantasies by, for example, coming up cold in the search for genes associated with most of the heritability of common illnesses (Zuk et al. 2012). When a recent highly publicized study, performed partly at the institute founded by the bioentrepreneur Craig Venter, reported a set of computer simulations of the biology of a bacterium under the gene-triumphalist title “A Whole-cell Computational Model Predicts Phenotype from Genotype,” this very claim was explicitly disavowed in the first pages of the same article (Karr et al., 2012).

Venter holds patents on numerous genes and gene-related technologies and has purchased the rights to many more. It is thus in his financial interest to persuade his funders and licensees—which include, at multi-hundred million dollar levels, the Exxon Corporation and the U.S. Department of Defense—that “life is a DNA software system” (Venter 2012a) and there is “no difference between digital code and genetic code” (Venter 2012b), despite the increases in knowledge and understanding about the complexities of gene function since Schrödinger made his enthusiastically naïve pronouncement and Baltimore (at the threshold of the Human Genome Project research and biobusiness bonanza) made his more calculated one. The claim to predict phenotype from genotype is in the same vein. But as Venter’s efforts (and those of his cohorts in food- and fuel-related corporations) to privatize

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1“The whole-cell model therefore presents a hypothesis of an emergent control of cell-cycle duration that is independent of genetic regulation.” (Karr et al. 2012, 392)
and reconfigure increasing swaths of the natural world have accelerated (see Newman 2009, 2012), gene-determinist views have gone into a sharp decline in the basic biological sciences. Much new work supports the recent assertion by an evolutionary biologist that “[t]he model of heredity now emerging is pluralistic, or ‘inclusive’ or ‘extended,’ in that it combines genetic and nongenetic mechanisms of inheritance” (Bonduriansky 2012).

The gene’s role in specifying the subunit arrangement of RNA, and indirectly, of proteins, recognized since the 1960s, has turned out to be much less straightforward than originally thought. But this alone does not account for its dethronement as the “secret of life” (a claim by Francis Crick upon his discovery with James Watson of the double helical structure of DNA; Watson 1968, 197). In fact, the reason genes were elevated to this status in the first place was based more on a mechanistic ideology that was already on the wane in the physical sciences than on any evidence for their generative powers (Newman 2003).

The gene-centrism of 20th century biology was a hundred years in the making, so it is no surprise that it has proven difficult to dislodge (Rose 1997). It is also no help that the broader culture is reliably friendly to obfuscation that favors commercial interests. The standard history is that the seminal discoveries of the great 19th century naturalists Gregor Mendel (1822–1864) and Charles Darwin (1809–1882) were melded into the Modern Evolutionary Synthesis in the period between the 1930s and 1950, a framework that with only minor embellishments over the intervening years could account entirely for the variety of life forms on earth. Then when the structure of DNA was elucidated in the early 1950s, organism-level biology fell into place with the Synthesis providing, in the form of molecular genetics, both an understanding-in-principle of the functioning of living things and the means to transform them, and ourselves, to new purposes.

This picture, though widely accepted, is more wrong than right. It is helpful to revisit some of the questions that concerned Mendel and Darwin but were side-stepped in formulating the Synthesis. The failure to resolve those important issues has provided much of the impetus for the recent challenges to, and downgrading of, the gene concept.

Mendel, the originator of the science of genetics, inferred associations of hypothetical “elements” with major features of the pea plant, such as whether the pod was inflated or constricted, or the peas wrinkled or smooth. Mendel also studied other plants with different inheritance properties, but in the case of peas at least, the elements (later called genes) had large effects on the organism’s phenotype. Mendel did not speculate on how they might exert these effects; that is, he had no theory of development. Such a theory would provide a scientific account of “characters,” which besides the pea plant features mentioned above, include such things as the segmentation of earthworms and the human backbone, the arrangement of bones in the hand, and the color patterns on a butterfly wing.
Mendel’s striking observation that the differentiating elements that organisms harbor could be manifested in offspring with very distinct, abruptly appearing phenotypic differences was not incorporated into the Synthesis. This is because this observation undermined the importance of Darwin’s mechanism of natural selection, which held that the gradual accumulation over long time periods of minor heritable phenotypic alterations, each marginally better adapted to their environment than their immediate predecessors, had produced all complex forms.

Darwin devised a more specific theory for the determination and inheritance of characters. He proposed the existence of particles—"gemmules"—that embodied, at a microscopic level, the characteristics of the different organs. He maintained that gemmules accumulated in the sexual organs and were passed along with the egg and sperm from one generation to the next. Darwin (like Pierre Louis Maupertuis [1698–1759] who had earlier proposed a similar theory; Cobb 2006) believed that the influence of external conditions on the gemmules’ potency and numbers was responsible for variations between organisms.

Darwin voiced his conviction that acquired characteristics could be inherited (a phenomenon since recognized as entirely compatible with ordinary biological processes; Jablonka and Raz 2009) with increasing force over his career. But it was left out of the Synthesis, which in a muscular 1950s-style formulation came to valorize “hard” (i.e., untouched by externalities) over “soft” inheritance. The contemporaneously emerging knowledge of DNA’s structure, its role in protein specification, and its means of propagation, made it the ideal exclusive medium of hard inheritance. The doctrine of inheritance of acquired characteristics was thus expunged from standard accounts of Darwin’s intellectual legacy in concert with his elevation to his present iconic position in mainstream biology. Apart from the theoretical requirements of the Synthesis, this also helped to cleanse him of contamination by the earlier theorist Jean-Baptiste Lamarck (1744–1829). During the Cold War, the French naturalist served as an ideological surrogate for the Soviet suppression of genetics in support of their voluntarist agricultural policies, and although he was the originator of scientific evolution, Lamarck has remained one of the most vilified figures in the history of science (Newman and Bhat 2011).

What the Synthesis ultimately drew from Darwin was the notion of the slow refinement and remolding of form by multiple cycles of natural selection. But harnessing Mendel’s genetics to this adaptive gradualism required an intellectual contortion act. As we have seen, Mendel associated his elements with sharply distinct character versions. The gradualist Mendelism of the Modern Synthesis, in contrast, associates genes with marginally different phenotypes. In order to keep Mendelism and Darwinism lashed together in a single theory, gene variants of “large effect”—like those Mendel actually studied—were written out of the theory and claimed to make no contribution to evolutionary change.
Mendel’s experiments, with their starkly different phenotypic outcomes dependent on the presence of one or another variant of a factor, were sometimes enlisted to support the incorrect notion that the factors “cause” or generate the relevant characters. This misinterpretation is dispelled when gene function is understood in the context of the dynamical properties of the complex systems in which genes operate (see below). But notwithstanding efforts in this direction by such pre-Synthesis theorists as William Bateson (1861–1926), D’Arcy W. Thompson (1860–1948), and Ernest Everett Just (1883–1941), the formulaters of the Synthesis rejected this approach. Indeed, some of their writings actually encouraged the “gene = character” misconception, despite the fact that in the Synthesis only the incremental variations in phenotype resulting from alterations in genotype are considered significant. Any causal role of genes in generating characters is an unexamined assumption of the theory.

Julian Huxley (1887–1975) in *Evolution: The Modern Synthesis*, a founding document of the framework, asserted the importance of the doctrine that “mendelian inheritance was universal” (Huxley 2010 [1942], 25). And while the invocation of Mendelism has been an unvarying refrain in this paradigm, what is meant is only vaguely related to Mendel’s differentiating elements. Writing retrospectively in 1982 about the origins of the Synthesis in his *Growth of Biological Thought*, Ernst Mayr (1904–2005), another of the theory’s architects, focused on what he claimed to be Mendel’s discovery of “particulate inheritance” and stated that the latter’s major contribution to biology was “[h]is inference that each character is represented in the fertilized egg by two, but only two, factors, one derived from the father and the other from the mother, and that these could be different” (Mayr 1982, 714).

Insofar as Mayr’s characterization of Mendelism as particulate inheritance is accurate, though, it does not apply to the vast majority of phenotypic characters. Most biological features are the collaborative products of many genes (“multifactorial”) that work in conjunction with non-genetic factors, such as (in the case of morphological characters) tissue-molding physical forces and effects mobilized by the products of the genes in the cells and cell masses in which they operate (Forgacs and Newman 2005). Even for abnormal conditions like sickle cell disease or cystic fibrosis, where the associated genes have been characterized down to the exact nucleotide subunits that are altered, the severity or even the presence of the disease state are unpredictable, because they depend on other genes and nongenetic factors. In no sense, then, are actual characters “represented” in the fertilized egg by two, and only two, factors.

This has not been lost on genetic scientists, who have increasingly recognized that most aspects of the phenotype are not inherited according to the laws that Mendel
devised to summarize his pea plant results. The phrase “non-Mendelian inheritance” appears in the National Library of Medicine’s PubMed database 329 times in papers listed since 1914, but half of those entries are from the last decade. The phenomenon has not become more prevalent, only more acknowledged. On the other hand, the lazy elision found in much of the modern popular and even scientific discussions of genetics, positing genes “for” such things as language (Cohen 1998) and aggressive behavior (Perbal 2012), is a continuing legacy of the gene-centrism of the Synthesis.

There is, in fact, one component of biological systems whose inheritance exactly conforms to Mayr’s definition of Mendelian inheritance: DNA sequences themselves, including those classically identified as genes (because they specify proteins by way of RNA intermediates), those that specify RNA molecules which do not encode proteins, and those which in the recent past have been considered “junk” (because they have no coding function at all). Since they are passed on from each parent to every organism resulting from sexual reproduction, segments of DNA above a critical length are indeed present in the fertilized egg in two versions, “one derived from the father and the other from the mother.” But the connection to the phenotype of the vast majority of DNA sequences is obscure, differing across biological contexts (referred to as “genetic backgrounds” in the standard gene-centric parlance.) While the Synthesis often defines evolution as populational changes in DNA sequence variants over time, this is now being perceived as a problem by some working in this paradigm. Indeed, one such scientist recently lamented, “the depth of our knowledge of genomes [i.e., the totality of the genes characteristic of specific organisms] is approaching completeness, whereas our knowledge of phenotypes remains, by comparison, minimal” (Houle 2010).

Whereas pre-Synthesis biology considered the entire sequence of events involved in the development of an organism from embryo to adult (“ontogeny”) and the origination of new types and species (“phylogeny”) to be intimately related (the same term, “evolution” was often used for both in the 19th century; Richards 1992), the Synthesis explicitly disavows the relevance of embryology. This was true at the outset: Thomas Hunt Morgan (1866–1945; himself formerly an embryologist), who received the Nobel Prize for his discoveries on the role of the chromosomes in heredity, wrote as the Synthesis was taking form: “The theory of the gene is justified without attempting to explain the causal processes that connect the genes and the characters” (Morgan 1926, 26). And it remains so now. A prominent theorist and defender of the Synthesis wrote nearly 80 years later, “our understanding of the molecular basis of development—however fascinating and important in revealing the hidden history of what has happened in evolution—sheds little light on what variation is potentially available for the use of selection” (Charlesworth 2005). Thus the custodians of Darwin’s legacy have explicitly relinquished his goal (embodied in the “gemmule”

3See also Dekkers and Hospital (2002) for the role of the “phenotypically uninformative gene” in agricultural science.
hypothesis) of providing an explanatory account of the systems of environmentally responsive biological qualities that are the actual objects of evolution.

Embryology—“developmental biology” in contemporary science—continued to take up the question of the “causal processes that connect the genes and the characters” virtually independently of evolutionary considerations, at least until recently. During the century of the dominance of Morgan-style genetics, developmental biology has shown that DNA, far from issuing unidirectional orders to the rest of the cell and organism, is acted upon not only by DNA-encoded molecules, but also by non-genetic factors, some of which originate in the external environment (Gilbert and Epel 2009). One classic example from the 1950s is the development of cervical vertebrae in mice. Different strains have different “genetically determined” numbers of neck bones, but gestating the embryos of one strain in the uterine environment of the other can override the difference made by the genes and produce mice with the characteristic number of the foster mother’s strain (McLaren and Michie 1958).

The interactions of genes with the factors that regulate them during development are highly nonlinear; continuous causes often lead to discontinuous effects. This is due to such genes being functionally interconnected in circuits and networks that exhibit limited numbers of discrete behaviors, where the behaviors are things like the folding or layering of tissues, or the differentiation of cells, for example into muscle, bone, blood, and so forth. The Synthesis does not deny that genes can interact with each other, but its gradualist bias considers this developmentally ubiquitous phenomenon the exception (and gives it a special name: “epistasis”), with genes contributing their small effects to the phenotype independently of one another (“additive inheritance”) being the rule. But highly integrated, nonlinear systems (i.e., actual gene networks) do not change gradually when mutated but typically jump between their various states in an abrupt fashion.

Genes are also subject to reversible (that is, nonmutational) chemical modifications that affect their levels of expression (i.e., functional activity). An example of this kind of “epigenetic” regulation is imprinting, where the function of the version of a given gene contributed by one of the two parents is suppressed in the normal course of development by a chemical “mark.” Such activity-altering DNA marking can also be influenced by the external environment. Maternal grooming and nursing of rat pups, for example, can chemically mark certain behavior-related genes so as to cause the same behavior to be exhibited by the female pups when they become mothers (Weaver et al., 2004). This transgenerational inheritance of behavioral traits is therefore propagated epigenetically, not genetically. In addition, a recent study of newborn identical twins found that the gene marking patterns in two different tissues (the only ones tested) were discordant, sometimes dramatically so, between the individuals (Gordon et al. 2012). This implies that the expression of the marked genes in at least these tissues, and most likely others, was also different, rendering the genetically identical infants biologically nonequivalent.
The idea of a guiding role for genes is further undermined when these epigenetic studies are considered along with new knowledge of protein structure. Thus, while no one disputes the usual textbook account that information in some DNA sequences is used by cells to specify the amino acid sequences of protein molecules, and that it is proteins that mediate most of the activities of embryos and mature organisms, it has long been assumed that the structure and function of proteins are uniquely determined by their sequences. This assumption has been disconfirmed by the recognition that at least 30 percent of the proteins in animals and plants are ‘‘intrinsically unstructured’’ and acquire their shapes and biological activities in the context of the presence of other proteins in their subcellular locales (Uversky 2011). Thus, individuals with many shared genes (even those having identical genomes) are biologically distinct in ways that are unpredictable from their DNA.

Developmental biology has mounted additional challenges to the assumptions of the Synthesis on the terrain of evolution itself (Robert 2004; Laubichler and Maienschein 2007; Müller 2007). Contrary to expectations that phenotypic change will passively track changes in genotypes over time, the phenomenon of ‘‘developmental systems drift’’ (True and Haag 2001) shows that a character’s phenotype, and even that of a class of organism (Schierenberg 2006), can remain essentially stable phenotypically over eons despite profound alterations in the underlying genetic circuitry of the generative processes. The possibility, mentioned above, of abrupt changes in form resulting from the nonlinear developmental effects of genetic change—or of no change at all, owing to morphological stasis in the face of developmental systems drift—implies an evolutionary pattern of ‘‘punctuated equilibria’’ (Gould and Eldredge 1977), contrary to the predictions of the Synthesis.

Many developmental biologists and philosophers of biology have thus concluded that there is more to heredity than simply genes, and they are increasingly advocating various forms of the earlier-spurned ‘‘soft’’ inheritance (Moss 2003; Gorelick and Laubichler 2008; Bonduriansky 2012). But some scientists, influenced by the decades-old cult of the gene, continue to overinflate its capabilities. Taking their cue from Erwin Schrödinger (see the first paragraph of this column), for example, they refer to genetic ‘‘programs’’ or ‘‘blueprints’’ for development, or even ‘‘genomic computers’’ (Istrail, De-Leon, and Davidson 2007). Writing for popular audiences, they frequently go further in imputing agency to genes, suggesting, for instance, that genes can ‘‘learn new tricks’’ (Carroll 2012). The emerging field of ‘‘synthetic biology,’’ with its ambitions to remake microbes, plants and animals on the basis of the newly recognized dynamical properties of multigene networks, has nonetheless also shown itself to be susceptible to misconceived metaphors from the world of computers and games (Newman 2012).

Given that heredity according to the Synthesis is indifferent to the causal connections of genes to the characters they are supposed to ‘‘represent,’’ there is some

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irony in reports that the allied field of populational medical genetics has been “flummoxed” by the “paradox of missing heritability” (Maher 2008). This phrase describes the observation that despite the fact that characters like height and traits like schizophrenia and autism are estimated to be 80–90 percent heritable, the majority of variant genes predicted to be associated with these conditions cannot be identified (Maher 2008). A recent state-of-the-art mathematical analysis of the genetics of human disease has come to the conclusion that the genes are not missing at all. Rather, contrary to the assumptions of standard (development-oblivious) Synthesis models, the genes that contribute causally to the relevant phenotypes interact with each other, and do so in nonlinear ways (Zuk et al., 2012). This comes as no surprise to anyone with a basic knowledge of development.

A series of papers on studies performed by a consortium of research groups called ENCODE that appeared in September 2012 provide the beginnings of an understanding of the complex interactions within the genome itself that defeat any straightforward assignment of DNA segments to unique organismal functions. Huge numbers of noncoding sequence motifs within an organism’s genome previously thought to be inessential “junk DNA” turn out to be conditional sites of regulation of distant coding sequences. The presence of these regulatory associations vary between types of cells and tissues and depend on geometric and topological relationships of the sites in addition to their sequences (Pennisi 2012). According to one of the principal ENCODE scientists, “These findings force a rethink of the definition of a gene and of the minimum unit of heredity” (Ecker et al. 2012).

The gene is thus down, but not entirely out. The recognition that a concept lacks validity does not necessarily prevent examples of it from being bought and sold (see, for example, slavery and financial derivatives). Because of genes’ utility as predictors of some degree of susceptibility to certain diseases, particularly in inbred subpopulations, ownership of the right to use specific gene sequences as diagnostics can represent major profit centers for biotechnology companies. The awarding of patents on DNA sequences has been controversial on both legal and human rights grounds. Gene patents, which have been easily obtainable for the last two decades using the most routine strategies, have been legally contentious, because such sequences are part of nature. They conflict with human rights since the cost of genetic tests is beyond the means of many patients, who must then pass on requesting them and sometimes die from the lack of otherwise readily available information.

Myriad Genetics of Utah, to take one example, holds more than 20 patents on the sequences and uses of the BRCA1 and 2 genes, whose encoded proteins participate in the uses and repair of DNA in the cell nucleus. The two BRCAs are among approximately 2000 (of a total of less than 25,000) human genes that have been granted U.S. patents. For reasons that are not entirely clear, mutations in these genes predispose women of some subpopulations, but not others, to a markedly increased risk of breast and ovarian cancers. The company’s patents allow it to enforce the requirement that the only laboratories permitted to test and sequence the
genes are ones affiliated with Myriad. Aside from placing obstacles to peer-reviewed validation of the tests, this restriction also imposes a large cost every time any of the genetic tests is used by a physician (Carbone et al. 2010).

The BRCA patents were contested in a 2009 lawsuit by professional medical organizations, doctors, and patients represented by the American Civil Liberties Union and the Public Patent Foundation of the Benjamin N. Cardozo School of Law. The following year there was a technical decision in the plaintiffs’ favor based on the judge’s opinion that isolated gene sequences constituted unpatentable subject matter. But Myriad’s main patent claims were ultimately upheld in August 2012 on appeal to the Federal Circuit Court (Marshall 2012), and the Myriad case is now before the U.S. Supreme Court, to be decided during the 2012–2013 term.

Craig Venter, mentioned at the beginning of this column, is the ideal companion to the gene in its declining days. Like the gene of the Synthesis, he is a supposed locus of implausible capabilities⁵ that can engender miraculous results (Hylton 2012) and embodies the notion that anything is possible in biology.⁶ However, with even Venter’s own colleagues unable to swallow overblown claims for the powers of the gene (Karr et al. 2012; see also footnote 1, above), there is reason to expect that scientific progress will ultimately relegate the obsolete conception of it that has fortified his particular brand of snake oil to a long-delayed oblivion.

References


⁵“We’re actually building what I call a digital biological converter, much in the same way a phone converts digital information into sound. You could email somebody a cell to make energy, to make food” (Venter 2012a).
⁶“No too many things excite my imagination as trying to design organisms—even people—for long term space flight, and perhaps colonization of other worlds” (Venter 2011). DNA testing, the business model of Myriad Genetics and similar companies, however limited or variable its efficacy, is a diagnostic, not a manipulative, technology. Venter’s promotion of his commercial activities by hyping his goal of prenatally modifying prospective people, apart from its scientific dishonesty, encourages a flippant attitude toward the Nuremberg Code on permissible human experimentation (http://en.wikipedia.org/wiki/Nuremberg_Code). See Newman 2010 for a discussion of delusions of human genetic engineering.


