The Gene

A Needed Revolution

Craig Holdrege

This short essay is about the gene. I have gathered many statements about this central concept of modern biology from geneticists and from historians and philosophers of science. The quotes I cite here are like footprints, indicating the pathway and evolution of modern genetics. A fascinating biography of a concept emerges. And, as I will try to show, the results of research in the past few decades have brought biology to a threshold that calls for a long-needed revolution in the way we interpret life.

The concept of the gene was first conceived by Gregor Mendel in the 1860s. He never used the term "gene," but spoke of "factor," "Anlage," or "element" to point to the underlying cause of differences in inherited characteristics of different offspring. He writes, for example:

> *The distinguishing characteristics of two plants can only be due to the differences in the make-up and grouping of those elements that stand in vital interaction within the germ cells.*
>
> Gregor Mendel (1866)

In 1909, Danish biologist Wilhelm Johannsen coined the term "gene" to refer to discrete determiners of inherited characteristics:

> *The word gene is completely free of any hypothesis; it expresses only the evident fact that, in any case, many characteristics of the organism are specified in the germ cells by means of special conditions, foundations, and determiners which are present in unique, separate, and thereby independent ways—in short, precisely what we wish to call genes.*
>
> Wilhelm Johannsen (1909)

Most people today are familiar with the term "gene" and have learned in school and through media that genes determine the characteristics of organisms. There are genes for hair and eye color, genes that direct the formation of our body's substances, and many genes that are somehow defective and cause disabilities and illnesses—genes for diabetes, cancer, schizophrenia, and more. No one talks about human, animal or plant physiology today without ascribing a central role to genes.

This deterministic gene is essentially the gene of the first half of the twentieth century. It is the gene most people have in mind today, over a half a century later. This gene has been described in the following terms:

> *In a specified environment, genes determine what kind of an individual a representative of a given species is going to be. There can be little doubt that genes also determine to what species a given individual will belong. By logical extension, it can be argued that genes determine whether an organism is a plant or an animal, as well as what kind of a plant or animal. And, to carry these deductions still further, genes determine whether or not an organism is going to develop at all.*
>
> Geneticists A.H. Sturtevant and G.W. Beadle (1939)

> *Mendelian inheritance is essentially atomistic, the heritable qualities of the organism behaving as if they were determined by irreducible particles (we now [1956] call them genes).*
>
> Geneticist Norman H. Horowitz (1956)

> *It has been known since about 1913 that the individual active units of heredity—the genes—are strung together in one-dimensional array along the chromosomes, the thread-like bodies in the nucleus of the cell.... In recent years it has become apparent that the information-containing part of the chromosomal chain is in most cases a giant molecule of DNA.*
>
> Geneticist Seymour Benzer (1962)

The Watson-Crick double helix-model of DNA (1953) and subsequent discoveries from the late 1950s into the 1970s relating DNA to protein synthesis provided a mechanistic model of the gene and of gene action that inaugurated the age of molecular biology. This was the time of boundless optimism concerning the ability of the reductionist approach to decipher the mechanism of life. As James Watson stated in his classic and influential textbook, *The Molecular Biology of the Gene*:

> *We have complete confidence that further research of the intensity given to genetics will eventually provide man with the ability to describe with completeness the essential features that constitute life.* (1973)

With advances in geneticists' knowledge, gene action has come to be viewed as an increasingly complex process, so that to state what a gene is requires longer statements filled with technical terms that no one but a specialist can understand. Witness the definition in their comprehensive textbook about the gene by Singer and Berg:

> *A [eukaryotic] gene is a combination of DNA segments that together constitute an expressible unit, expression leading to the formation of one or more specific functional gene products that may be either RNA molecules or polypeptides. The segments of a gene include (1) the transcribed region (the transcription unit), which encompasses the coding sequences, intervening sequences, any 5' leader and 3' trailer sequences that surround the ends of the coding sequences, and any regulatory segments included in the transcription unit, and (2) the regulatory sequences that flank the transcription unit and are required for specific expression.*
>
> Biochemists Maxine Singer and Paul Berg (1991)

But the advances in genetics have not only refined the mechanistic model. The complexity at the molecular level reveals that the simple mechanisms one imagined in the 1960s simply do not exist in that form. It has become less and less clear what a gene actually is and does. And although the deterministic gene is still the gene that lives in the minds of many students, lay people, and—at least as a desire—in the minds of many biologists, the findings of late twentieth century genetics show one thing clearly: the simple deterministic gene, the foundational "atom" of biology is dead. There is no clear-cut hereditary mechanism—no definite sequence of nitrogenous bases in a segment of a DNA molecule that determines the make-up and structure of proteins, which in turn determine a definite feature of an organism.

What follows is a series of statements about the contemporary gene—the gene of the past two decades. This gene looks very different from one described above:

> *The more molecular biologists learn about genes, the less sure they seem to become of what a gene really is. Knowledge about the structure and functioning of genes abounds, but also, the gene has become curiously intangible. Now it seems that a cell's enzymes are capable of actively manipulating DNA to do this or that. A genome consists largely of semi-stable genetic elements that may be rearranged or even moved around in the genome thus modifying the information content of DNA. Bits of DNA may be induced to share in the coding for different functional units in response to the organism's environment. All this makes a gene's demarcation largely dependent on the cell's regulatory apparatus. Rather than ultimate factors, genes begin to look like hardly definable temporary products of a cell's physiology. Often they have become amorphous entities of unclear existence ready to vanish into the genomic or developmental background at any time.*
>
> Peter Beurton (historian of science),
> Raphael Falk (geneticist) and
> Hans-Jörg Rheinsberger (historian of science) (2000)

> *The gene is no longer a fixed point on the chromosome…producing a single messenger RNA. Rather, most eurkaryotic genes consist of split DNA sequences, often producing more than one mRNA by means of complex promoters and/or alternative splicing. Furthermore, DNA sequences are movable in certain respects, and proteins produced by a single gene are processed into their constituent parts. Moreover, in certain cases the primary transcript is edited before translation, using information from different genetic units and thereby demolishing the one-to-one correspondence between gene and messenger RNA. Finally, the occurrence of nested genes invalidates the simpler and earlier idea of the linear arrangement of genes in the linkage group, and gene assembly similarly confutes the idea of a simple on-to-one correspondence between the gene as the unit of transmission and of genetic function….*
>
> Geneticist Peter Portin (1993)

> *Whether a particular gene is perceived to be a major gene, a minor gene or even a neutral gene depends entirely on the genetic background in which it occurs, and this apparent attribute of a gene can change rapidly in the course of selection on the phenotype.*
>
> Developmental biologists H. Frederik Nijhout
> and Susan Paulsen (1997)

The preceding descriptions point to the contextual nature of the gene: if you "have" a gene at one point in time, it may become, both structurally and functionally, something quite different at another time or place. As a result, it is no longer possible to speak of the gene in a straightforward manner:

> *There is a fact of the matter about the structure of DNA, but there is no single fact of the matter about what the gene is. [Genetics today] provides strong, concrete support for the claim that the concept of the gene is open rather than closed with respect to both its reference potential and its reference.*
>
> Philosopher of science Richard M. Burian (1985)

> *Paradoxically, in spite of the new, sometimes overwhelming, concreteness of our comprehension of the gene as a result of DNA technology, we seem to be left with a rather abstract*

and generalized concept of the gene that has quite different significances in different contexts.… It should, however, be strongly emphasized that our comprehension of the very concept of the gene has always been abstract and open as indicated already by Johannsen [in 1909].

Geneticist Peter Portin (1993)

[In the molecular gene concept] 'gene' denotes the recurring process that leads to the temporally and spatially regulated expression of a particular polypeptide product…the gene is identified not with these DNA sequences alone but rather with a process in whose context these sequences take on a definite meaning.

Paul Griffiths (philosopher of science) and Eva Neumann-Held (biologist and philosopher of science) (1999)

Because the gene has become something so very different from the clearly circumscribed determinant it started out as, some geneticists think it is time to leave it behind:

For biological research, the twentieth century has arguably been the century of the gene. The central importance of the gene as a unity of inheritance and function has been crucial to our present understanding of many biological phenomena. Nonetheless, we may well have come to the point where the use of the term "gene" is of limited value and might in fact be a hindrance to our understanding of the genome. Although this may sound heretical, especially coming from a card-carrying geneticist, it reflects the fact that, unlike chromosomes, genes are not physical objects but are merely concepts that have acquired a great deal of historic baggage over the past decades.

Geneticist William Gelbart (1998)

Our knowledge of the structure and function of the genetic material has outgrown the terminology traditionally used to describe it. It is arguable that the old term gene, essential at an earlier stage of the analysis, is no longer useful, except as a handy and versatile expression, the meaning of which is determined by the context.

Geneticist Peter Portin (1993)

The gene concept, I believe, is unlikely to be discarded, since it is far too deeply entrenched in the minds of scientists and the public. But we need to realize that the popular usage of the term, which still implicates the gene as the definitive causative agent in biology, simply does not coincide with biological reality.

As geneticist Peter Portin remarks in one of the above quotes, "the very concept of the gene has always been abstract." In other words, the gene is not a thing at all, but a way of ordering and interpreting phenomena. This may be surprising to anyone used to thinking about genes as concrete biological substances that make things happen. The gene as a robust "thing" is a figment in the materialist mind, a mind that can only conceive the world as governed by mindless material entities that (somehow) carry out meaningful processes.

I do not want to suggest that the concept of the gene has no relation to material happenings. But the gene concept was not, in the first place, derived from engagement in the richness of hereditary phenomena. It was a pre-conceived notion that framed scientists' thinking and action. Experiments were designed with the gene concept in mind, and investigators then interpreted the results in terms of the particulate conception of inheritance they presupposed in the first place. In the best case (for example, Mendel's experiments with peas or many experiments in the early twentieth century with the fruit fly), experiments showed a partial fit with the conceptual framework. Researchers homed in on the fit and delved ever more into biological minutiae. The gene concept opened up worlds and seemed to be supported by a great number of experiments.

As different researchers pursued a variety of directions of inquiry, the phenomena at the molecular level showed increasing complexity and variation. As a result, any schematic representation of the gene just didn't work, and a colorful array of definitions of the gene emerged, as the above quotes show.[1] In view of the plethora of gene definitions, philosopher of science Philip Kitcher concludes:

A gene is anything a competent biologist has chosen to call a gene. (1992)

This statement does not indicate a fall into total relativism. It is simply the indirect acknowledgement on the part of contemporary genetics that there is no particular *this* (gene) determining a particular *that* (trait). So to retain a connection to the actual phenomena, geneticists have come to describe the gene as a potential, as a process, and as dependent on the organismic context. In other words, the mechanistic conception of the gene as a power unto itself, elevated above the turmoil and complexity of day-to-day cellular life and doing its thing under any and all

1. I'd be remiss if I didn't mention that the history of genetics, from the early twentieth century on, provides many examples of observations and experimental results that did not fit with the dominant gene paradigm. But only within the past couple of decades has the evidence become so glaring that it can no longer be ignored by the scientific establishment.

conditions, has to be discarded. Scientists are trying to adapt the static gene concept to the dynamic reality of the organism.

A great gift of recent genetic studies is that they show in a rich and varied way at the microlevel what we could have known all along from a study of organismic life at the macrolevel if our minds had been open: every organism develops from an open potential and forms over time in dynamic interaction with its own developmental process and its (changing) environment. Only insofar as the mechanistic paradigm holds the human mind captive do we come to think of and believe in genes as neatly circumscribed material determinants.

The gene is an abstraction—a product of a process of isolation, as neurologist Kurt Goldstein would have said—that has guided the development of genetics for over a century. The idea of a fundamental unit of inheritance, the idea of the grand mechanism that determines life, a mechanism that the human mind can fathom and eventually control, has fired the minds of modern geneticists.

But the research itself—the immersion in the phenomena mined from living organisms via experimentation—brings scientists and their concept of the gene to a boundary. It is a boundary one can ignore, as is largely the case in commercialized genetic engineering. It is a boundary that can stimulate scientists to tweak existing models to better fit experimental results. But it is also a boundary that can be felt existentially and become a stimulus for a mental and methodological revolution:

* Can we take reality so seriously that we actually give up—in our heart of hearts and in our innermost thought forms—rigid conceptions like that of the gene?
* Can we do without the security of a guiding notion that imagines discrete entities working in chains of cause and effect to constitute the stuff of life?
* Can we get beyond the "thing" mindset altogether, which is informed by fixed concepts, and learn to consciously swim in and adapt ourselves to a new medium, namely the fluidity and dynamics of the organic world?

These are radical questions. If we answer them with "yes," and our swimming exercises begin in earnest, we will encounter wholly new facets of the world. It seems to me that the phenomena themselves are calling for this revolution.

References

Benzer, Seymour (1962). "The Fine Structure of the Gene," *Scientific American,* January, 1962 (reprint: p. 2).

Beurton, Peter, J., Raphael Falk and Hans-Jörg Rheinsberger (Eds.) (2000). "Introduction," in *The Concept of the Gene in Development and Evolution*. Cambridge: Cambridge University Press, pp. ix-xiv.

Burian, R. M. (1985). "On Conceptual Change in Biology: The Case of the Gene," in *Evolution at a Crossroads: The New Biology and the New Philosophy of Science*, Depew, D. J. and B. H. Weber (Eds.). Cambridge: MIT Press, pp. 21-42.

Gelbart, William. (1998). "Databases in Genomic Research," *Science* vol. 282, pp. 659-661.

Griffiths, Paul E. and Eva M. Neumann-Held (1999). "The Many Faces of the Gene," *BioScience* vol. 49, pp. 656-662.

Horowitz, Norman H. (1956). "The Gene," *Scientific American,* October, 1956 (reprint: p. 4).

Johannsen, W. (1909). Quoted in Portugal, F., and J. Cohen (1978). *A Century of DNA*. Cambridge: MIT Press, p. 118.

Kitcher, P. (1992). "Gene: Current Usages." In *Keywords in Evolutionary Biology*, Keller, E. F. & E. A. Lloyd (Eds.). Cambridge: Harvard University Press, pp. 128-131.

Mendel, Gregor (1866). *Versuch über Pflanzenhybride*. Reprint, 1913. Leipzig: Wilhelm Engelman, pp. 1-46. (Quote translated by Craig Holdrege.)

Nijhout, H. F. and S. M. Paulsen (1997). "Developmental models and polygenic characters," *American Naturalist* vol. 149, pp. 394–405.

Portin, Peter (1993). "The Concept of the Gene: Short History and Present Status," *The Quarterly Review of Biology* vol. 68, pp. 173-223.

Singer, M. and P. Berg (1991). *Genes and Genomes: A Changing Perspective*. Mill Valley: University Science Books, p. 622.

Sturtevant, A.H. and G.W. Beadle. (1939 [1962]). *An Introduction to Genetics.* New York: Dover, p. 334.

Watson, James (1973). *The Molecular Biology of the Gene,* third edition. Menlo Park, California: The Benjamin/Cummings Publ. Co.