The (Dual) Origin of Epigenetics

D. HAIG

*Department of Organismic and Evolutionary Biology, Harvard University,
Cambridge, Massachusetts 02138*

"Epigenetics" has different meanings for different scientists. Molecular biologists are probably most familiar with a definition of epigenetics as "*the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence*" (Riggs et al. 1996). For them, epigenetic mechanisms would include DNA methylation and histone modification. Functional morphologists, however, would be more familiar with a definition such as that of Herring (1993), for whom epigenetics refers to *"the entire series of interactions among cells and cell products which leads to morphogenesis and differentiation."* She continues that "among the numerous epigenetic factors influencing the vertebrate face is mechanical loading" and that "epigenetic influences range from hormones and growth factors to ambient temperature and orientation in a gravitational field." In this note, I will argue that these disparate definitions have come about because "epigenetics" had at least two semi-independent origins during the 20th century.

The adjective "epigenetic" has a much longer history than the noun "epigenetics" because the adjective originally referred to a different noun, "epigenesis." Thus, the Oxford English Dictionary gives the primary sense of *epigenetic* as "[o]f or pertaining to, or of the nature of epigenesis" and defines *epigenesis* as "the formation of an organic germ as a new product" with *the theory of epigenesis* defined as "the theory that the germ is brought into existence (by successive accretions), and not merely developed, in the process of reproduction." It is not my purpose here to delve into the history of theories of epigenesis, except to note that "epigenetic" is sometimes still used in this earlier sense as pertaining to epigenesis.

Epigenetics was coined by Waddington (1942) to refer to the study of the "causal mechanisms" by which "the genes of the genotype bring about phenotypic effects." Waddington (1939 [p. 156]) had earlier used epigenotype to refer to "the set of organizers and organizing relations to which a certain piece of tissue will be subject during development." He believed that genotype and phenotype referred to "differences between whole organisms . . . [and were] not adequate or appropriate for the consideration of differences within a single organism." Thus, epigenetics for Waddington referred to a subject similar to what we would now call developmental biology.

Waddington (1956) later provided some insight into his reasons for choosing epigenetics. He wrote, "The fact that the word 'epigenetics' is reminiscent of 'epigenesis'

is to my mind one of the points in its favour. . . . We all realize that, by the time development begins, the zygote contains certain 'preformed' characters, but that these must interact with one another, in processes of 'epigenesis', before the adult condition is attained. The study of the 'preformed' characters nowadays belongs to the discipline known as 'genetics'; the name 'epigenetics' is suggested as the study of those processes which constitute the epigenesis which is also involved in development" (see also Waddington 1939 [pp. 154–155]).

Waddington targeted what he saw as the naive view of many geneticists that there was a simple correspondence between genes and characters. For Waddington, the course of development was determined by the interaction of many genes with each other and with the environment. Neo-Darwinism, he believed, involved "a breach between organism and nature as complete as the Cartesian dualism of mind and matter; an epigenetic consideration of evolution would go some way toward healing it" (Waddington 1953 [p. ix]). Waddington decried "the reigning modern view . . . [that] the direction of mutational change is entirely at random, and that adaptation results solely from the natural selection of mutations which happen to give rise to individuals with suitable characteristics." This he considered to be an "extremist" theory (Waddington 1953 [p. 151]). Because Waddington claimed to provide a richer paradigm for studying the interaction between organism and environment than the impoverished view of genetics, an epigenetic approach has appealed to critics of evolutionary "orthodoxy," whether these be biologists who feel that there is something lacking in the neo-Darwinian synthesis (see, e.g., Løvtrup 1972; Ho and Saunders 1979; Jablonka and Lamb 1989) or philosophers who favor a less gene-centric, more holistic, view of biology (see, e.g., articles in van de Vijver et al. 2002).

Waddington's term gained few converts prior to the 1960s. A notable exception was Huxley (1956) who encouraged others to use epigenetics to mean "the science of developmental process in general." Later, in a review of cancer biology, Huxley (1957) used epigenetics "to denote the analytic study of individual development (ontogeny) with its central problem of differentiation." For Huxley, "The method by which tissues and organs differentiate in the course of normal development is at the moment the main blank space in biology's map. . . . [W]e know little of the precise steps taken by epigenetic processes, of the biochemical factors involved, and above all,

of what determines the replicable specificity of differentiated tissues." Thus, epigenetics was concerned with the processes by which a constant genotype gave rise to differentiated cell types and tissues, and perturbations of which could give rise to cancer.

Berry and Searle (1963) initiated an association of "epigenetics" with the study of variation in skeletal development. They used epigenetic "in Waddington's sense, to emphasize the developmental origin of the discontinuities being studied, with genetic factors determining the main features of the 'epigenetic landscape' but environmental forces influencing the final outcome." Their study of the rodent skeleton was later extended to a study of epigenetic variation in the human cranium (Berry and Berry 1967). Herring's (1993) definition of epigenetics (quoted in the first paragraph of this paper) is a direct descendant of this usage.

The second 20th-century derivation of "epigenetics" can be traced to Nanney (1958). At a conference in Gif-sur-Yvette on Extrachromosomal Heredity (March 1958), Nanney contrasted what he called genetic and *paragenetic* systems. However, Pontecorvo told Nanney of the criticism he had received from a professor of Greek for Pontecorvo's use of the term *parasexuality* (Ephrussi 1958). By the time the published version of Nanney's remarks appeared in July 1958, Nanney had substituted epigenetic for paragenetic and added references to Waddington (Nanney 1958). This history indicates that Nanney's concept of what he came to call epigenetic control systems was independent of Waddington's prior use of epigenetics, but that Nanney considered their two usages to be compatible.

Nanney (1958) started his comments by noting the great recent advances of chemical genetics. These advances had allowed a consistent hypothesis in which genetic control systems were based on a "template replicating mechanism" that determined the "library of specificities." However, he believed that "auxiliary mechanisms with different principles of operation are involved in determining which specificities are to be expressed in any particular cell." These auxiliary mechanisms he called epigenetic control systems. He saw them as accounting for the observation that cells with the same genotype could have different phenotypes. Moreover, epigenetic regulation could show properties of long-term persistence. Therefore, "the observation of indefinite persistence of differences does not distinguish persistent homeostasis due to DNA maintenance (genetic homeostasis) from persistent homeostasis due to epigenetic regulation (epigenetic homeostasis)." He contrasted "[t]he current concept of a primary genetic material (DNA), replicating by a template mechanism" with "a homeostatic system operating by, perhaps, self-regulating metabolic patterns."

It is no coincidence that Nanney made his remarks at a conference on Extrachromosomal Heredity. Nanney was a significant protagonist in what Sapp (1987) has styled the struggle for authority in genetics. On one side of this conflict were geneticists who ascribed a predominant role in heredity, evolution, and development to the genetic material of the nucleus. On the other side were biologists,

such as Nanney, who wished to maintain an important role for the cytoplasm, or extranuclear factors, in hereditary. Nanney (1957 [p. 136]) had earlier expressed his views on the relative roles of the nucleus and cytoplasm in political terms, and these comments give some insight into his favored model of epigenetic control systems:

> Two concepts of genetic mechanisms have persisted side by side . . . The first of these we will designate the "Master Molecule" concept. . . . In its simplest form the concept places the "master molecules" in the chromosomes and attributes the characteristics of an organism to their specific construction; all other cellular constituents are considered relatively inconsequential except as obedient servants of the masters. This is in essence the Theory of the Gene, interpreted to suggest totalitarian government. . . .
>
> The second concept of a genetic mechanism is one which is more difficult to describe . . . This concept we will designate as the "Steady State" concept. By the term "Steady State" we envision a dynamic self-perpetuating organization of a variety of molecular species which owes its specific properties not to the characteristics of any one kind of molecule, but to the functional interrelationships of these molecular species. . . . In contrast to the totalitarian government by "master molecules," the "steady state" government is a more democratic organization, composed of interacting cellular fractions operating in self-perpetuating patterns.

By the time of the Cold Spring Harbor Symposium on Quantitative Biology, Nanney (1959) had refined his conception of epigenetic systems. These he characterized as "signal interpreting devices, yielding predictable results in response to specific stimuli from inside and outside the cell. They are conceived as the integrative systems regulating the expression of genetic potentialities; mutual exclusion, simultaneity of expression, and adaptive cellular transformation could scarcely be achieved without efficient triggering devices." He now conceded that epigenetic systems were "presumably limited by the information contained in the genetic library. . . . An epigenetic change should not result in a permanent loss of information and a return to a previous condition of expression is always theoretically possible."

Boris Ephrussi, one of the organizers of the conference in Gif-sur-Yvette, had long been interested in questions of cell heredity and was another proponent of an important role for extrachromosomal inheritance. Ephrussi championed Nanney's concept of epigenetic control at a conference on Genetic Approaches to Somatic Cell Variation held in Gatlinburg, Tennessee (April 1958). Ephrussi (1958) distinguished between "truly genetic mechanisms" based on "the transmission of particles carrying their own structural information" from "epigenetic mechanisms involving functional states of the nucleus." He adopted the terms genetic and epigenetic because they more clearly delimited "the notion of true genetic change. This is a concession on my part, and many of my geneticist friends will, I am sure, enjoy the shift of my stand. Unfortunately, I must remind them that, as a corollary, we must admit that not everything that is inherited is genetic."

In his summary comments to the Gatlinburg conference, Lederberg (1958) was not prepared to accept this olive branch without qualification. In Lederberg's view, Ephrussi wished to distinguish between genetic information that was structural from epigenetic information that was based on a dynamic flux equilibrium. But many properties that Ephrussi would ascribe to epigenetic mechanisms could also be explained by structural changes in the nucleus. Lederberg was prepared to "define a category of genetic information as being 'nucleic'; that is, depending on the *sequence of nucleotides* in a nucleic acid. By contrast, 'epinucleic' information is expressed in another form, e.g., as an aspect of nucleic acid configuration other than nucleotide sequence or in polypeptide or polyamine adjuncts to the polynucleotide." Offering his own olive branch, Lederberg was prepared to concede an adjunct role for "extranucleic information in molecules or reaction cycles not directly connected with nucleic acid." (Lederberg considered Ephrussi's choice of terms "confusing if only because 'epigenetic' is already widely current in a different sense, e.g., in Waddington's book 'The Epigenetics of Birds.'")

Lederberg's concept of epinucleic information is close to the concept of epigenetic modification used in modern molecular biology whereas Nanney's appeal to cytoplasmic steady states led nowhere. Ironically, Lederberg's terminology of nucleic, epinucleic, and extranucleic information obtained few converts whereas Nanney's dichotomy of genetic and epigenetic control was adopted by several researchers, especially those interested in cell heredity of somatic cells and cancer. For example, Harris (1964 [p. 1]) cited Nanney for a distinction between genetic changes that "depend on a recasting of hereditary determinants" and epigenetic changes that "take place against a constant cellular genome." In his view, "Truly genetic mechanisms are concerned with the preservation and replication of information in structural form" whereas epigenetic mechanisms "regulate the expression of genetic information. They serve to translate structural symbols into phenotypic reality."

During the 1960s, one can find a number of researchers working on cell culture or cancer who implicitly or explicitly derive their distinction between epigenetic and genetic processes from either Nanney or Harris (see, e.g., Waymouth 1967; Braun 1969 [p. 153]). The fact that Cahn and Cahn (1966) could refer to the epigenetics of development in clonal cell culture without providing an explicit definition or citation for "epigenetics" suggests that the authors expected the term would be understood by most of their intended audience. Markert (1968a) similarly provided no citation for "epigenetic" when he concluded that "there is probably no gene coding for cancer per se. Instead, normal gene activity is misprogrammed by epigenetic mechanisms to produce a neoplastic pattern of metabolism in which all of the individual components are normal."

Another early use of an epigenetic/genetic distinction occurred in the burgeoning field of protein electrophoresis. Soon after Nanney distinguished epigenetic from genetic control, Markert and Møller (1959) introduced "the term *isozyme* to describe the different molecular forms in which proteins may exist with the same enzymatic specificity. . . . The existence of isozymes raises the question of whether each of these also is controlled by a separate gene or whether they are all modifications of a single gene product." Nanney's terminology was ready-made to distinguish these alternatives. Thus, Markert (1968b) distinguished "the genetic control of final conformation through specifying amino acid sequences [from] epigenetic direction of conformational folding or subunit association" (also see Allen 1960; Ruddle and Roderick 1965; Munkres 1968).

Widespread use of epigenetics to refer to heritable changes that do not involve changes in DNA sequence did not occur until the 1990s, but I will leave my historical survey in the 1960s and limit myself to some brief comments on subsequent changes in usage based on a less systematic search of the literature. Since the 1960s, the evolving meaning of epigenetics in molecular and cellular biology has coexisted with continued use of epigenetics in a Waddingtonian sense, with the different definitions sometimes conflated and thought to represent a single coherent discipline (Jablonka and Lamb 2002; Müller and Olsson 2003). Holliday (1979) contains the earliest description of DNA methylation as an "epigenetic" process that I have found, but I suspect that "The inheritance of epigenetic defects" (Holliday 1987) was the critical paper that lit the fuse for the explosion in use of "epigenetic" in the 1990s.

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