“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 meioticallyheritable 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 favor. . . . 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 naıve 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 desired “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.” Thus he considered it 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 differentia-
ted tissues." Thus, epigenetics was concerned with the processes by which a constant genotype gave rise to dif-
ferentiated 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 de-
velopment. They used epigenetic “in Waddington’s
sense, to emphasize the developmental origin of the dis-
continuities being studied, with genetic factors determin-
ing the main features of the “epigenetic landscape” but en-
vironmental 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 de-
scentant 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 par-
agenetic systems. However, Pontecorvo told Nanney of
the criticism he had received from a professor of Greek
in heredity, evolution, and development to the genetic
conflict were geneticists who ascribed a predominant role
in the struggle for authority in genetics. On one side of this
organization of a variety of molecular species which
owns its specific properties not to the characteristics of any one kind of molecule, but to the functional interrela-
tionships of these molecular species. . . . In contrast to the totalitarian government by “master molecules,” the
“steady state” government is a more democratic organi-
ization, composed of interacting cellular fractions operat-
ing in self-perpetuating patterns.

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
owns its specific properties not to the characteristics of
any one kind of molecule, but to the functional interrela-
tionships of these molecular species. . . . In contrast to the totalitarian government by “master molecules,” the
“steady state” government is a more democratic organi-
ization, composed of interacting cellular fractions operat-
ing in self-perpetuating patterns.

By the time of the Cold Spring Harbor Symposium on
Quantitative Biology, Nanney (1959) had refined his con-
ception 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 regu-
lating the expression of genetic potentialities; mutual ex-
clusion, simultaneity of expression, and adaptive cellular
transformation could scarcely be achieved without effi-
cient triggering devices.” He now conceded that epige-
netic systems were “presumably limited by the informa-
tion contained in the genetic library. . . . An epigenetic
change should not result in a permanent loss of informa-
tion 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 impor-
tant role for extrachromosomal inheritance. Ephrussi
championed Nanney’s concept of epigenetic control at a
conference on Genetic Approaches to Somatic Cell Vari-
ation held in Gatlinburg, Tennessee (April 1958). Ephrussi (1958) distinguished between “truly genetic
mechanisms” and “signal directing 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.”

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In his summary comments to the Gatinburg 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, ‘epimolecular’ information is expressed in another form, e.g., as an aspect of nucleic acid configuration other than nucleotide sequence or in polypeptide or polynucleotide adjuncts to the poly nucleotide.” Offering his own olive branch, Lederberg was prepared to concede an adjutant role for “extra-nuclear 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 epimolecular 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, epimolecular, and extramolecular 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 phenotype 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 genetic and epigenetic processes from either Nanney or Harris (see, e.g., Waymouth 1967; Braun 1969 [p. 153]). The fact that 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 phenotype reality.”

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 (isose) to describe the different molecular forms in which proteins may exist with the same enzymatic speci city. . . . 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 Olofson 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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The (Dual) Origin of Epigenetics

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Access the most recent version at doi:10.1101/sqb.2004.69.67

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