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## The Epidemiology of Epigenetics

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<b>Citation</b>	Haig, David. 2012. The epidemiology of epigenetics. <i>International Journal of Epidemiology</i> 41(1): 13-16.
<b>Published Version</b>	<a href="http://dx.doi.org/10.1093/ije/dyr183">dx.doi.org/10.1093/ije/dyr183</a>
<b>Accessed</b>	February 19, 2015 12:04:05 PM EST
<b>Citable Link</b>	<a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:10859960">http://nrs.harvard.edu/urn-3:HUL.InstRepos:10859960</a>
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# **The epidemiology of epigenetics**

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We are in the midst of an epidemic of the words *epigenetic* and *epigenetics*. In the database of ISI Web of Knowledge, more than 1300 articles published in 2010 contain epigenetic(s) in their title whereas the corresponding number for each year prior to 2000 is less than a hundred. Figure 1 illustrates the long term trend using an index designed to correct for changes in the size and composition of the database. Roughly speaking there was little change in relative frequency from the 1950s until 1999, but since then epigenetics has increased in each successive year, with a ten-fold increase from 1999 to 2009.

For more than a half-century, epigenetics has denoted a protean, difficult-to-define field, in part, because the word had at least two independent origins<sup>1,2</sup>. The earliest published use of epigenetics occurs in the article reprinted in this issue<sup>3</sup>. Here, Waddington proposed epigenetics as a name for studies of the “causal mechanisms” by which “genes of the genotype bring about phenotypic effects.” From the perspective of current debates about the meaning of epigenetics, Waddington’s article is notable for the lack of discussion of inheritance, although he does emphasize how early developmental events can have large effects on adult anatomy and physiology.

Waddington later clarified his intended meaning in his *Principles of Embryology*: epigenetics was “perhaps the most satisfactory expression” for the field variously known as *Entwicklungsmechanik* (developmental mechanics) or experimental embryology<sup>4</sup>. In a generally favorable review, Huxley noted Waddington retained embryology in the title of his book, however:

“A good title provides a banner under which a new scientific movement can advance (witness ‘gene’ and ‘genetics’ in the study of heredity). Accordingly I am going to have the courage of *his* convictions: I shall use ‘Epigenetics’ as meaning the science of developmental process in general, and hope that others will do the same.”<sup>5</sup>

In reply, Waddington commented: “It was not entirely from diffidence ... that I named my book the *Principles of Embryology*; I did so mainly because it devotes some space to the descriptive anatomical data related to development, and is not confined wholly to that analysis of causal mechanisms for which the name ‘epigenetics’ is appropriate.”<sup>6</sup>

The second origin of epigenetics traces to David Nanney’s *Epigenetic control systems*<sup>7</sup>. In this article, Nanney contrasted genetic and epigenetic control, with the latter

determining which volume in the library of genetic specificities was to be expressed in a particular cell. Nanney noted that “Epigenetic systems show a wide range of stability characteristics ... cells with the same genotype may not only manifest different phenotypes, but these differences in expressed potentialities may persist indefinitely during cellular division in essentially the same environment.” Thus, cellular heredity was a potential property of epigenetic systems but not a defining feature of such systems. Ephrussi adopted Nanney’s terminology but tied epigenetics more closely to cellular inheritance<sup>8</sup>. He wished to distinguish epigenetic mechanisms from “more trivial, immediately reversible phenotypic mechanisms” and reminded geneticists “that not everything that is inherited is genetic.” Luria distinguished between genetic and epigenetic somatic mutations as possible causes for the origin of cancer<sup>9</sup>.

Abercrombie used Nanney’s concept of epigenetic control to explain cellular differentiation<sup>10</sup>. He suggested ‘epigenotype’ might be used for “the set of self-reproducing regulatory mechanisms that characterizes each of the different tissue types of an organism.” In the appended discussion, Waddington remarked that he had earlier used epigenotype for a different concept but “The term is not much needed today in that sense and I am perfectly willing to give it up to somebody else!”<sup>10</sup>

By the 1980s epigenetics had developed distinct Waddingtonian and Nanneyan ‘traditions’, but the term did not form part of the everyday vocabulary of most biologists. The Waddingtonian tradition was concerned with the causal processes by which genetic systems interact with the environment to bring about development and phenotypic plasticity. The Nanneyan tradition distinguished between genetic and epigenetic causes of changes in cellular phenotype, including the transformation of somatic cells into cancer cells. The two traditions were loosely united by a common interest in how a constant genotype can produce different phenotypes. (I refer to the second tradition as Nanneyan even though Nanney’s founding role was largely forgotten. In recent years, the two traditions have become increasingly difficult to distinguish as they have spawned hybrid recombinant offspring<sup>11</sup>.)

Epigenetics became closely associated with DNA methylation in the 1990s catalyzed by the discovery of imprinted genes in mice and men. Holliday had earlier proposed that loss of methyl groups from nucleotide bases could cause a switch in gene

activity which would be heritable. He described the altered state of gene expression as an epigenetic change<sup>12</sup>. Later Holliday proposed that epigenetic defects in germ line cells could be inherited by offspring and proposed that “heritable changes based on DNA modification should be designated epimutations to distinguish them from classical mutations.”<sup>13</sup>

For a brief period, epigenetics and DNA methylation became almost synonymous, at least in the Nanneyan tradition, with heritability recognized as a *condicio sine qua non* of epigenetics. Influential definitions from this period are “Nuclear inheritance which is not based on differences in DNA sequence”<sup>14</sup> and “the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence”<sup>15</sup>. By the turn of the century, modification of histone proteins was proposed to be another mechanism of epigenetic inheritance<sup>16-18</sup>.

The label epigenetic was soon extended to include all transcriptional effects of chromatin modification whether or not these were inherited. Some decried this shift in meaning because no histone modification had been conclusively demonstrated to be heritable<sup>19</sup>. But, from a deeper historical perspective, heritability had not originally been a defining feature of epigenetic systems. More recently the definition of epigenetic mechanisms has been further expanded to include the regulatory actions of non-coding RNAs. Definitions have been modified to encompass the expanded domain of what qualifies as epigenetic. Recent definitions of epigenetics include: “the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states”<sup>20</sup>; “heritable changes in gene activity and expression (in the progeny of cells or of individuals) and also stable, long-term alterations in the transcriptional potential of a cell that are not necessarily heritable”<sup>21</sup>; and “phenotypic variation that is not attributable to genetic variation.”<sup>22</sup>

The choice of which word to use, from a smorgasbord of possible options, is a process that takes place, often subconsciously, in the privacy of individual minds. Therefore, reconstructions of the reasons why words rise and fall in use are inherently speculative. Two features of the time series of Figure 1 invite explanation. The first is the persistence of epigenetics as an infrequent term for almost 50 years: most newly-proposed scientific terms are stillborn. Epigenetic (the adjective) had a long history associated with

the noun epigenesis. Part of the staying power of epigenetics (the noun) may have been its explicit or implicit association with one side in the preformation vs. epigenesis debate. In addition, epigenetics had an enduring appeal for critics of genetic orthodoxy because the word's structure had connotations of being 'above' or 'beyond' genetics<sup>2,23</sup>. On the other hand, the existence of competing Nanneyan and Waddingtonian definitions may have contributed to the failure of either definition to be widely adopted.

The second feature to be explained is the meteoric rise in the use of epigenetics in the new century. The timing coincides with the shift in usage to include histone modification. Epigenetics has clearly provided a banner under which a new scientific movement has advanced. At the heart of this movement is research on the role of chromatin modification in the control of transcription. But the movement is a broad tent that unites studies of the effects of environmental toxins on gene expression, of the fetal origins of adult disease, and of how early rearing affects adult behavior. The indefinite definition of epigenetics (together with the connotation of being 'above' or 'beyond' genetics) has meant that scientists from divergent disciplines, studying only loosely-related phenomena, could all feel they were engaged in epigenetic research near the cutting edge of modern biology.

What does the future hold for the epigenetics? Will there be a struggle for legitimacy with attempts to restrict the use of the term to a narrower field? Will epigenetics become a general label for studies of gene regulation, broadly construed? Genetics provides a pertinent analogy of a label that covers a range of weakly-linked disciplines. Or will epigenetics be displaced by another buzz-word in the competition for grants, citations, and tenure?

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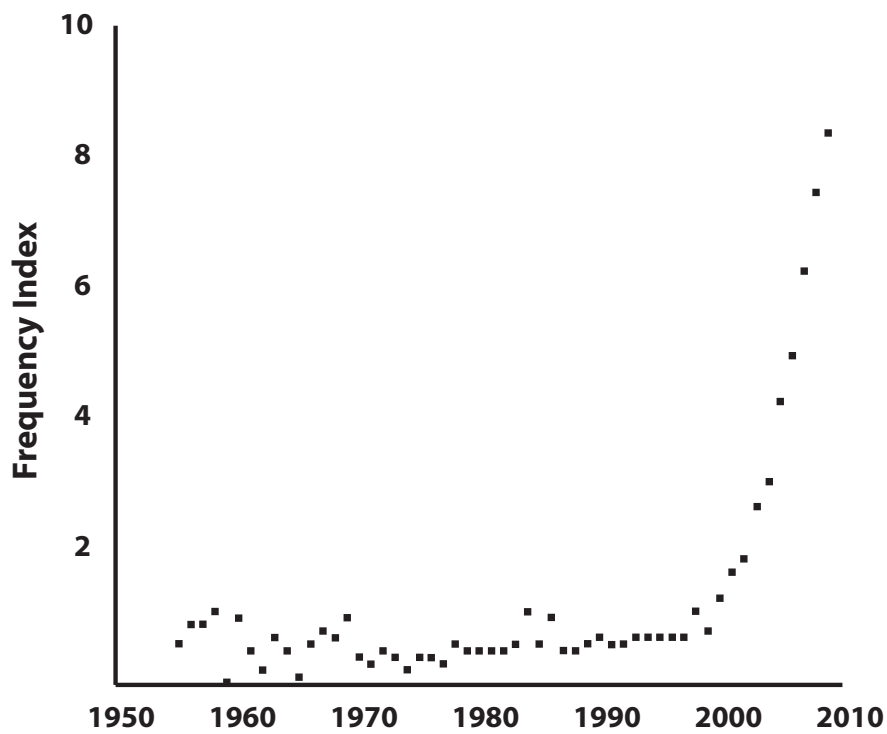


Figure 1: Relative frequency of articles with epigenetic or epigenetics in their title. The frequency index is the number of titles retrieved from the ISI Web of Knowledge using the search term epigenetic\* divided by the number of titles retrieved using genetic\* multiplied by 100. An index of one means there is one ‘epigenetic’ title for every 100 ‘genetic’ titles.